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

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Disclosure

- The author declares NO conflict of interest.

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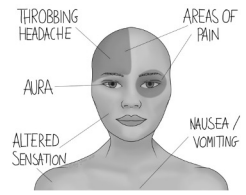

Migraines

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Migraines

- Complex disorder characterized by **episodes of moderate-to-severe headache** which 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.

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Proposed Criteria for Refractory Chronic Migraine

Criteria	Definition
A. Primary Diagnosis	1. ICHD-III chronic migraine 2. Medication overuse headache excluded*
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

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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 days in a month for >than 3 months and has migraine features on at least eight or more days in a month.
- **Probable migraine**: symptomatic migraine attack that lacks one of the features required to fulfill criteria for one of the above and does not meet the criteria for another type of headache

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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.

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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%

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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

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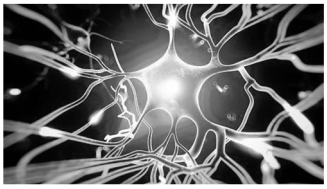

Interventional Options for Refractory Migraines
Nerve Blocks

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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 co-morbid 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 (CFSI)

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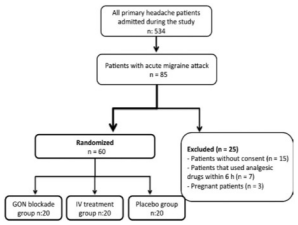
The effectiveness of greater occipital nerve blockade in treating acute migraine-related headaches in emergency departments *Acta Neurol Scand.* 2018;1–7.

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).



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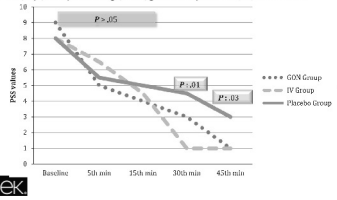
PSS [median (IQR 25%-75%)]	GON blockade group (n = 20)	IV treatment group (n = 20)	Placebo group(n = 20)	P
Baseline	9 (7.25-9.75)	8 (7-9)	8 (7-9.5)	.2
5th min	5 (3.25-8)	6.5 (5-7)	5.5 (5-7)	.7
15th min	4 (0-6.5)	4.5 (2.3-5)	5 (3-6)	.3
30th min	3 (0-4.75)	1 (0-4)	4.5 (1-6)	.01
45th min	1 (0-3)	1 (0-2)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

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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

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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%, resp.).
  - 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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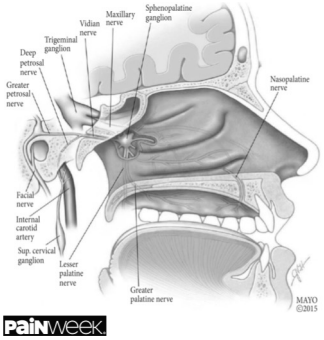

Pain Res Treat. 2018 May 7;2018:2516953.

The Sphenocath Device

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

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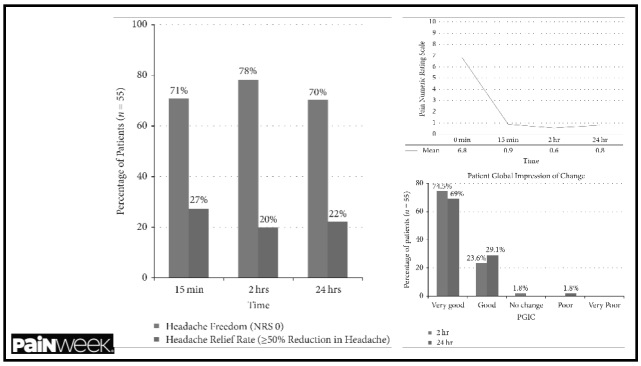

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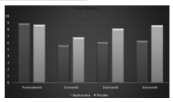
The efficacy of greater occipital nerve blockade in chronic migraine: A placebo-controlled study *Acta Neurol Scand* 2016; 1–7

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 four 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.



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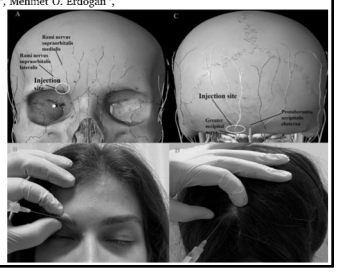
Comparison of greater occipital nerve and supra orbital nerve blocks methods in the treatment of acute migraine attack: A randomized double-blind controlled trial

Nihat M. Hokenek[b,*], Duygu Ozer[b], Erdal Yılmaz[a], Nurhayat Baskaya[a], Ummahan Dalkiliinc Hokenek[c], Rohat Ak[a], Ramazan Guven[d], Mehmet O. Erdogan[a], Lewis Aaron Mepham[f]

Clinical Neurology and Neurosurgery 207 (2021) 106821

- Technique:
  - injection to the Supra Orbital Nerve (**SON**) site shown in pictures A and B
  - injection to the Greater Occipital Nerve (**GON**) site shown in pictures C and D
- 128 patients in 4 groups: GON, SON, Combined, and Placebo



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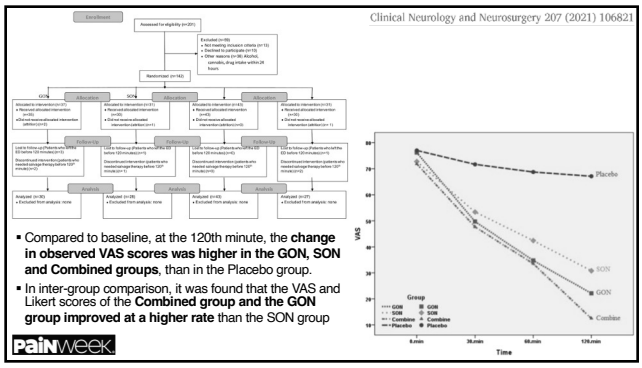

- Compared to baseline, at the 120th minute, the **change in observed VAS scores was higher in the GON, SON and Combined groups**, than in the Placebo group.
- In inter-group comparison, it was found that the VAS and Likert scores of the **Combined group and the GON group improved at a higher rate** than the SON group

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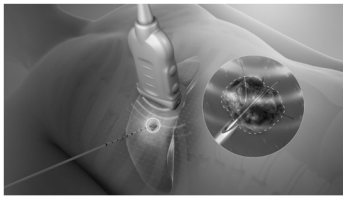

Interventional Options for Refractory Migraines
Radiofrequency, Steroid Injections

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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[i], Anthony R. Plunkett[h], Aubrey J. Verdun[h], Milan P. Stojanovic[j], Steven Hanling[m], Octav Constantinescu[n], Ronald L. White[n], Brian C. McLean[n], Paul F. Pasquina[n], and Zirong Zhao[e,f]
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 non-pain outcomes.

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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[§]

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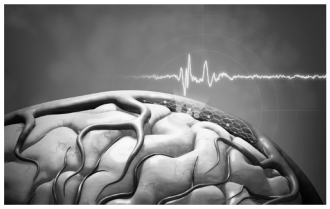

Interventional Options for Refractory Migraines
Neuromodulation

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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

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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.

Current Pain and Headache Reports (2019) 23: 68

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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

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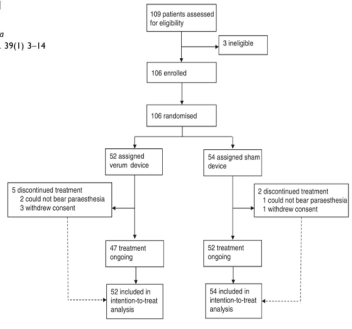
Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial *Cephalalgia* 2019, Vol. 39(1) 3–14

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.



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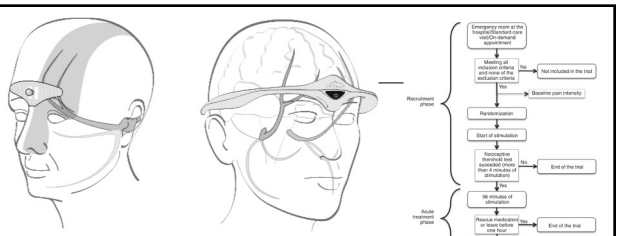

- Electrode positioning: (left) the electrode covers the supratrochlearis and supraorbitalis nerves, and (right) the neurostimulator device is placed on the forehead, and connected to the electrode.

Cephalalgia
2019, Vol. 39(1) 3–14

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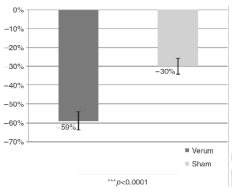
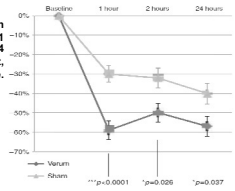
Cephalalgia
2019, Vol. 39(1) 3–14

- 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.



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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[3] 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)

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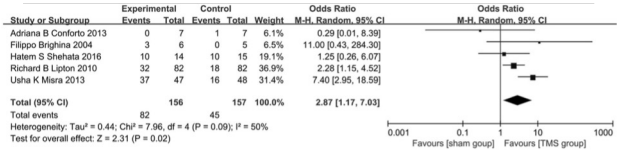
The Journal of Headache and Pain (2017) 18:86

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



- 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; $p = 0.02$).

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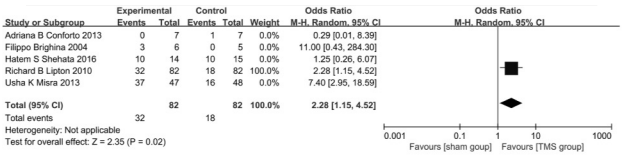
The Journal of Headache and Pain (2017) 18:86

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



- 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 h 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 ($p = 0.02$).

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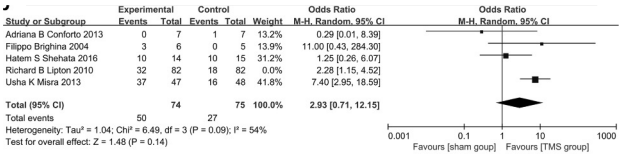
The Journal of Headache and Pain (2017) 18:86

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



- 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; $p = 0.14$).

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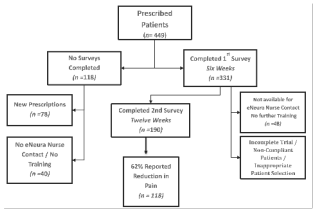
Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program **J Headache Pain. 2015;16:535.**

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



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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	43	45
15–20	56	36	37
21–25	14	12	9
26–30	58	57	44
Pain severity*	Baseline	6 weeks	12 weeks
0	0	3	2
1–3	0	14	63
4–6	32	85	75
7–9	140	54	47
10	18	7	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

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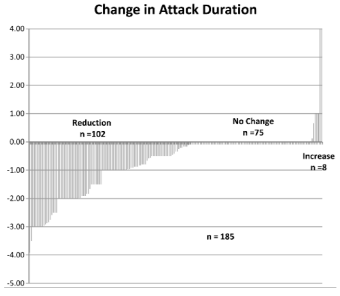
J Headache Pain. 2015;16:535.

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



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A Randomized Controlled Trial of High Rate rTMS Versus rTMS and Amitriptyline in Chronic Migraine

Pain Physician 2021; 24:E733-E741

Jayantee Kalita, MD, DM[1], Sumit Kumar, DM[1], Varun K Singh, DM[2], Usha K Misra, DM[2]

- High rate **repetitive transcranial magnetic stimulation (rTMS)** in patients with refractory chronic migraine
  - 41 patients in group I: 10 Hz rTMS
  - 42 in group II: rTMS and amitriptyline
- rTMS: Ten trains of 10 Hz rTMS, delivered per session. Three sessions were delivered on an alternate day and were repeated every month for 3 months.

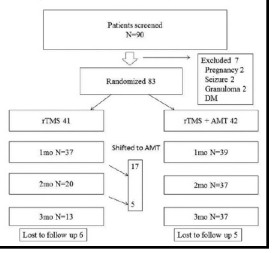

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Table 2. *Comparison of primary and secondary outcomes at 1, 2, and 3 months in CM patients receiving rTMS vs rTMS and AMT on intention to treat analysis.*

Primary outcome	rTMS (n = 41)	rTMS +AMT (n = 42)	*P* value
1 month			
> 50% freq ↓	11 (26.8%)	20 (47.6%)	0.069
> 50% VAS ↓	2 (4.9%)	9 (21.4%)	0.048
2 months			
> 50% freq ↓	12 (29.3%)	29 ((69%)	0.0004
> 50% VAS ↓	5 (12.2%)	14 (33.3%)	0.035
3 months			
> 50% freq ↓	13 (31.7%)	32 (76.2%)	< 0.0001
> 50% VAS ↓	8 (19.5%)	20 (47.6%)	0.01

Table 3. *Comparison of side effects of rTMS group vs rTMS and AMT group in patients with CM.*

Side effects	rTMS (n = 41)	rTMS + AMT (n = 42)	*P*
Rhinorrhea	4	4	0.97
Tearing	14	7	0.07
Pain	36	32	0.17
Noise	22	23	0.92
Dry mouth	5	11	0.64
Sedation	3	6	0.85

Combination of rTMS and amitriptyline is safe and more effective in chronic migraine compared to rTMS alone.

Pain Physician 2021; 24:E733-E741

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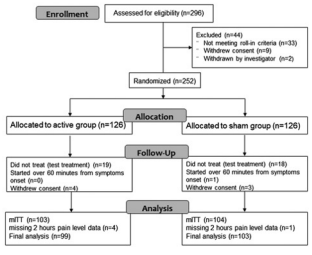
Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Headache 2019;59:1240-1252

David Yarnitsky, MD; David W. Dodick, MD; Brian M. Grosberg, MD; Rami Burstein, PhD; Alon Ironi, MSEE; Dugan 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.



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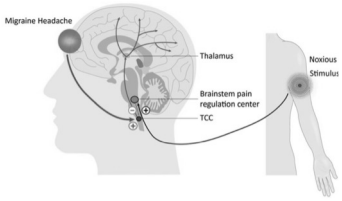
Headache 2019;59:1240-1252

- **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.



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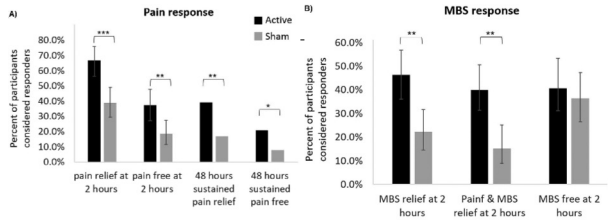
Headache 2019;59:1240-1252



- (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.

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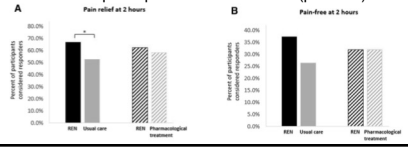
Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications *The Journal of Headache and Pain* (2019) 20:83

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 h post-treatment: pain relief was achieved in 66.7%** of the participants using REN versus 52.5% participants with usual care ($p < 0.05$)



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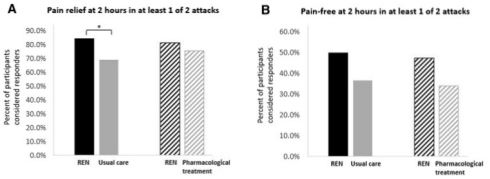
The Journal of Headache and Pain (2019) 20:83



- Pain relief at 2 h in at least one of two attacks was achieved by 84.4% of participants versus 68.9% in usual care ($p < 0.05$). REN and usual care were similarly effective for pain-free status at 2 h.

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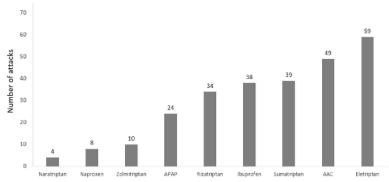
The Journal of Headache and Pain (2019) 20:83



- Number of participants using different types of acute pharmacological treatments in their first reported attack in the run-in phase.
- **Non-inferiority of REN compared with acute pharmacological treatments** and its non-dependency on preventive medication use.

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Tracking tDCS induced grey matter changes in episodic migraine: a randomized controlled trial

Simon Schading[1], Heiko Pohl[2], Andreas Gantenbein[2,3], Roger Luechinger[4], Peter Sandor[2,3], Franz Riederer[2,5], Patrick Freund[1,6,7†] and Lars Michels[8*†]

Schading *et al. The Journal of Headache and Pain* (2021) 22:139

- Objective: Track **longitudinally grey matter volume changes** in occipital areas in episodic migraineurs during and up to five months after **occipital transcranial direct current stimulation** (tDCS)
- 24 episodic migraineurs were randomized to either receive verum or sham tDCS treatment for 28 days
- Structural MRI performed at baseline (prior to treatment), 1.5 months and 5.5 months (after completion of treatment); 31 healthy controls were scanned with the same MRI protocol

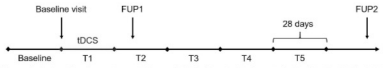

Fig. 1 Overview of the study design. The observation period was subdivided into six 28-day periods (Baseline, T1–5). The tDCS treatment was performed during T1 and was initiated immediately after the baseline visit. FUP1 was scheduled shortly after the end of the stimulation period and FUP2 after T5. Modified from Pohl et al., [32]

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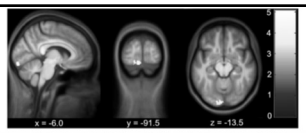
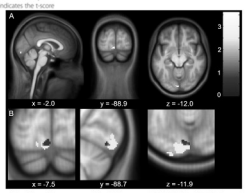


Fig. 2 Significant volumetric differences between migraine patients and healthy controls at baseline. Overlay of statistical parametric maps (uncorrected $p < 0.001$) shows increased cortical volume in patients versus controls in the left lingual gyrus. The color bar indicates the t-score

- Before treatment, patients reported **mean 5.6 monthly migraine days**. Grey matter volume ↕ in the left lingual gyrus in migraineurs compared to controls.
- 4 weeks of tDCS led to a **reduction of 1.9 migraine days/month** and was paralleled by grey matter volume ↓ in the left lingual gyrus in the treatment group; its extent overlapping with that seen at baseline.



Schading *et al. The Journal of Headache and Pain* (2021) 22:139

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Fig. 3 Significant quadratic differences between verum and sham tDCS group revealed by TBM. Overlay of statistical parametric maps (uncorrected $p < 0.001$) shows a significant quadratic difference in the left lingual gyrus (**A**). The color bar indicates the t-score. Comparison of the statistical parametric maps (uncorrected $p < 0.005$, for illustrative purposes) of the cross-sectional cluster (in yellow) and the longitudinal cluster (in red) reveals that the regions of both clusters in the left lingual gyrus overlap (**B**)

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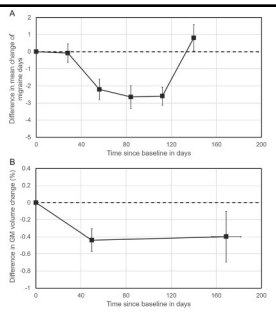

Fig. 4 Clinical and structural changes following tDCS treatment. Change in monthly migraine days depicted as difference in days between verum and sham tDCS group (**A**). Change in GM volume depicted as difference in percent between verum and sham tDCS group (**B**). Negative values represent less migraine days, respectively lower GM volume in the verum tDCS group compared to the sham tDCS group. All values are normalized to the baseline measurement

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Schading *et al. The Journal of Headache and Pain* (2021) 22:139

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Analgesic efficacy of a portable, disposable, and self-applied transcutaneous electrical nerve stimulation device during migraine attacks: A real-life randomized controlled trial

Pain Practice. 2021;21:850–858.

Flávia S. Domingues MSc[1] | Maisa V. Gayoso MSc[1] | Shafaq Sikandar PhD[2] | Leopoldo Muniz da Silva PhD[3] | Ronaldo G. Fonseca PhD[4] | Guilherme A. M. de Barros PhD[1]

- Aim: evaluate the efficacy of a **portable, disposable, at- home self-applied 20-min transcutaneous electrical nerve stimulation (TENS) device** during migraine attacks
- RCT conducted over 3 months, with monthly assessments; active placebos (sham group) allocated 1:1; 74 participants

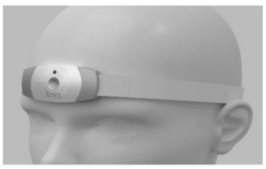

FIGURE 1 Disposable device used in the study that was placed over supraorbital nerves

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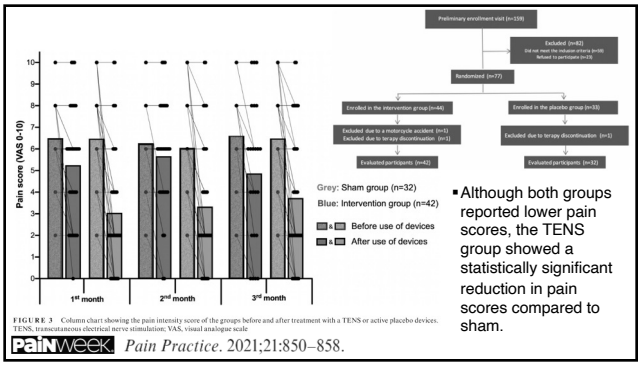

FIGURE 3 Column chart showing the pain intensity score of the groups before and after treatment with a TENS or active placebo devices. TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale

- Although both groups reported lower pain scores, the TENS group showed a statistically significant reduction in pain scores compared to sham.

PainWeek *Pain Practice*. 2021;21:850–858.

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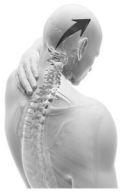

Cervicogenic Headaches

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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 one 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 three months after successful treatment of the causative disorder or lesion.

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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

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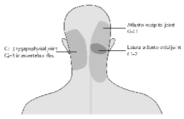
Cervicogenic Headache

- **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	Medial Atlantoaxial	
		Lateral Atlantoaxial	C2-C3 zygapophysial
			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

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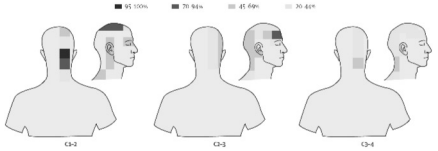
- Areas of pain relief in patients who underwent controlled blocks of the synovial joints at C1–2, C2–3, and C3–4
- The density of shading is proportional to the number of patients who perceived pain in the particular area indicated.



- 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.

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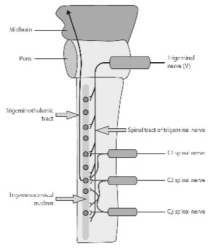
Cervicogenic Headache

- **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 three 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 three cervical spinal nerves.



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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	+		+	+

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Occipital Neuralgia and Cervicogenic Headache: Diagnosis and Management

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

Current Neurology and Neuroscience Reports (2019) 19: 20

- **Non-pharmacologic 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.

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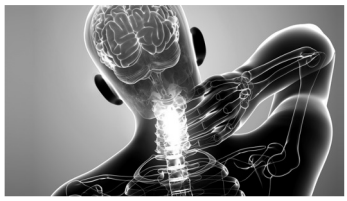

Interventional Options for Cervicogenic Headaches

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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 un-controlled 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.

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Occipital Neuralgia and Cervicogenic Headache: Diagnosis and Management

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

Current Neurology and Neuroscience Reports (2019) 19: 20

- **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.

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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

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Interventional Options for Cervicogenic Headaches
Nerve Blocks

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

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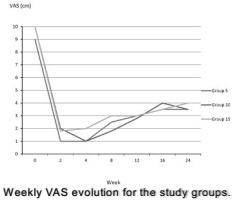
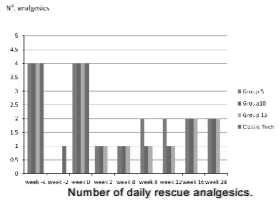
Pain Practice, Volume 15, Issue 7, 2015 654–661

- 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

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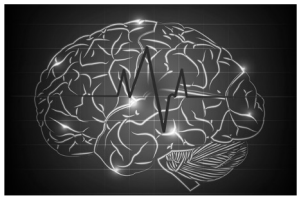

Interventional Options for Cervicogenic Headaches
Radiofrequency

PainWeek

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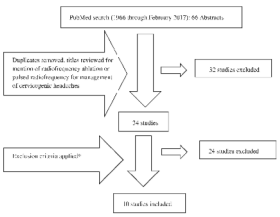
Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headaches

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.



PainWeek

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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.

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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.

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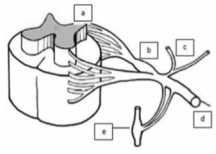
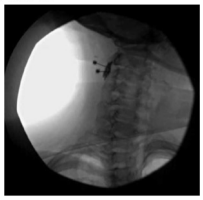
Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headache

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



- 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.

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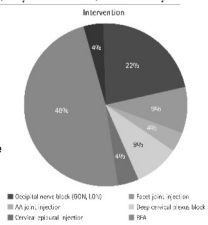
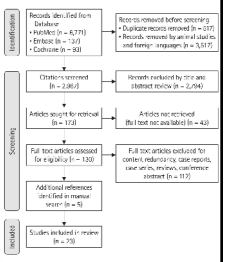
Efficacy of interventional treatment strategies for managing patients with cervicogenic headache: a systematic review

Korean J Anesthesiol 2022;75(1):12-24

Sonal Goyal[1,*], Ajit Kumar[1,*], Priyanka Mishra[1], Divakar Goyal[2]

- **Most of the studies reported pain reduction except 2 studies on RFA.**
- Occipital nerve blocks, cervical facet joint injection, AA joint injection, deep cervical plexus block, cervical epidural injection may be reasonable options in refractory CeH.
- RFA was found to have favorable long-term outcomes, while better safety has been reported with pulsed therapy.





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Interventional Options for Cervicogenic Headaches Neuromodulation

PainWeek

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

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

Neuromodulation. 20:8 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.
  - **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.

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 (50.0–80.0)	
HIT6 score, median (Q1–Q3)			
Overall (n = 16)	67.0 (56.0–74.5)	49.5 (40.0–57.3)	0.0025
Responders (n = 11)	66.0 (56.0–75.0)	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%)	

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

Marzieh Eghtesadi, MD [redacted]; 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.

- **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.

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)	
HIT-6 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%%)	

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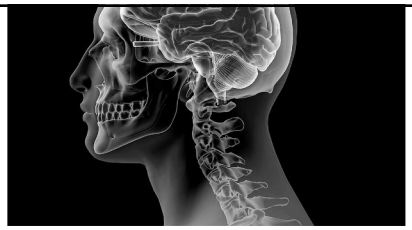

Interventional Options for Cervicogenic Headaches
Various Other Techniques

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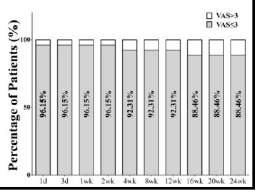
The Feasibility and Efficacy of Ultrasound-Guided C2 Nerve Root Coblation for Cervicogenic Headache

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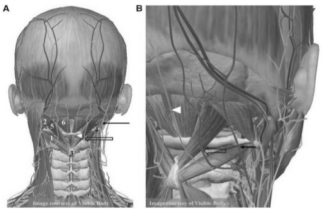
The Feasibility and Efficacy of Ultrasound-Guided C2 Nerve Root Coblation for Cervicogenic Headache

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

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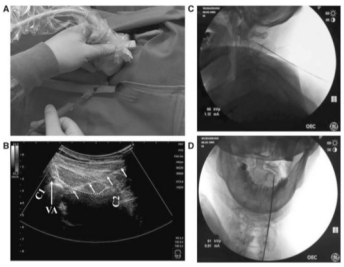
The Feasibility and Efficacy of Ultrasound-Guided C2 Nerve Root Coblation for Cervicogenic Headache

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

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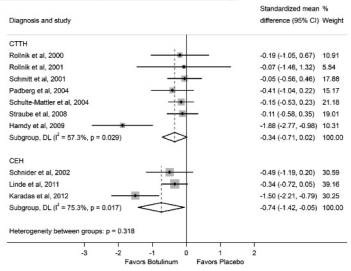
Sissel Breivold Roland, Are Hugo Pripp, Mbachi Ruth Msomphora and Gunnvald Kvarstein*

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

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



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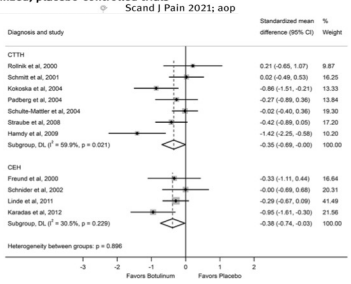
The efficacy of botulinum toxin A treatment for tension-type or cervicogenic headache: a systematic review and meta-analysis of randomized, placebo-controlled trials

Scand J Pain 2021; aop

- Standardized mean difference in **pain intensity** between botulinum toxin A versus placebo.



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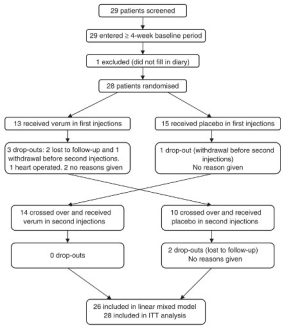
Onabotulinum toxin A treatment of cervicogenic headache: A randomised, double-blind, placebo-controlled crossover study Cephalalgia. 2011 May;31(7):797-807.

Mattias Linde[1,2], Knut Hagen[1,2], Øyvind Salvesen[3], Gøril Bruvik Gravdahl[4], Grethe Helde[1] and Lars Jacob Stovner[1,3]

- 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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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[3], Grethe Helde[1] and Lars Jacob Stovner[1,2]

- 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[a] (95% CI)	Mean difference after placebo[a] (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)	$p < 0.001$

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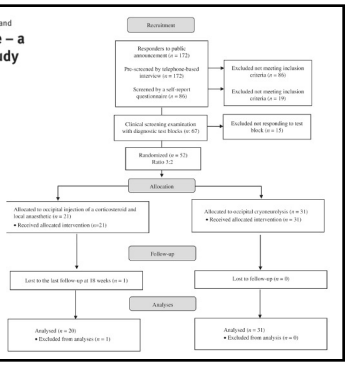
Gunnvald Kvarstein*, Henrik Högström, Sara Maria Allen and Jan Henrik Rosland

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 + bupicavaine



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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**.

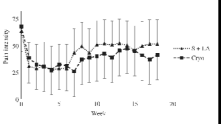

Table 2: Maximum headache intensity before and after treatment (*n*: 52).

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[c]	30	22		<0.001[c]	45	33		<0.001[c]
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		

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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.

- **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 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)

painweek

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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

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