Pharmacological management options for refractory orofacial pain

38th International AIGeDO Congress, Naples. 10th October 2025

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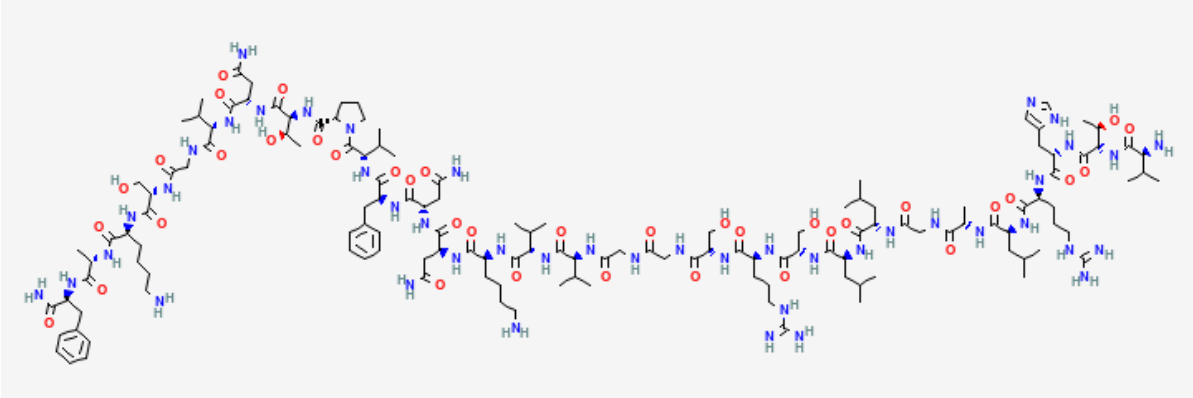
Diplomate of American board or orofacial pain

Aims/objectives

· Explore evidence base for **CGRP inhibitors** for refractory orofacial pain conditions.

· Discuss case examples to support treatment planning

What is Calcitonin gene-related peptide (CGRP) ?



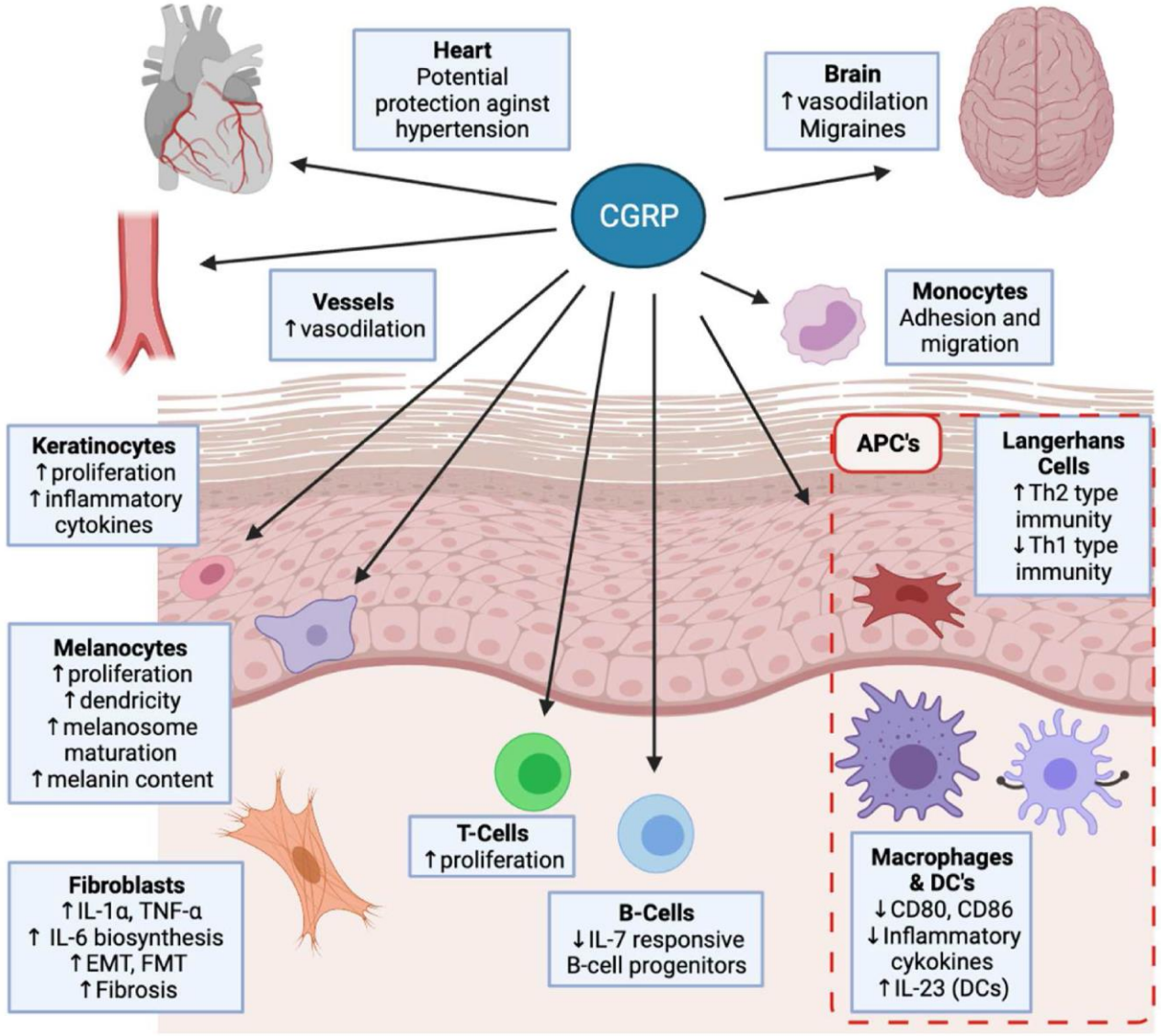
- Amino acid neuropeptide
- Sensory nerve fibers
  - C and Aδ
- **α-CGRP** and β-CGRP

Molecular formulae

$C_{139}H_{230}N_{44}O_{38}$

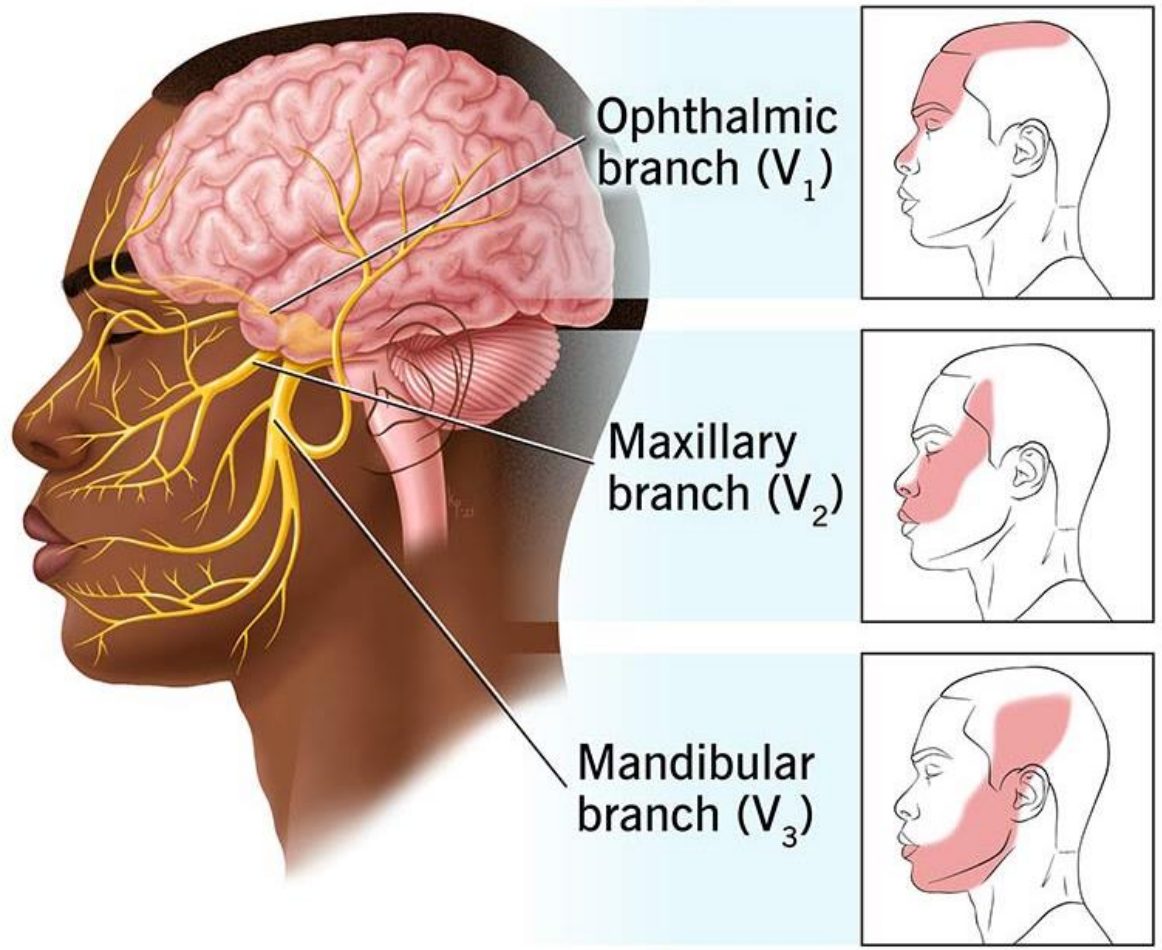
Calcitonin gene-related peptide (8-37) | C139H230N44O38 | CID 16134896 - PubChem

Roles of CGRP

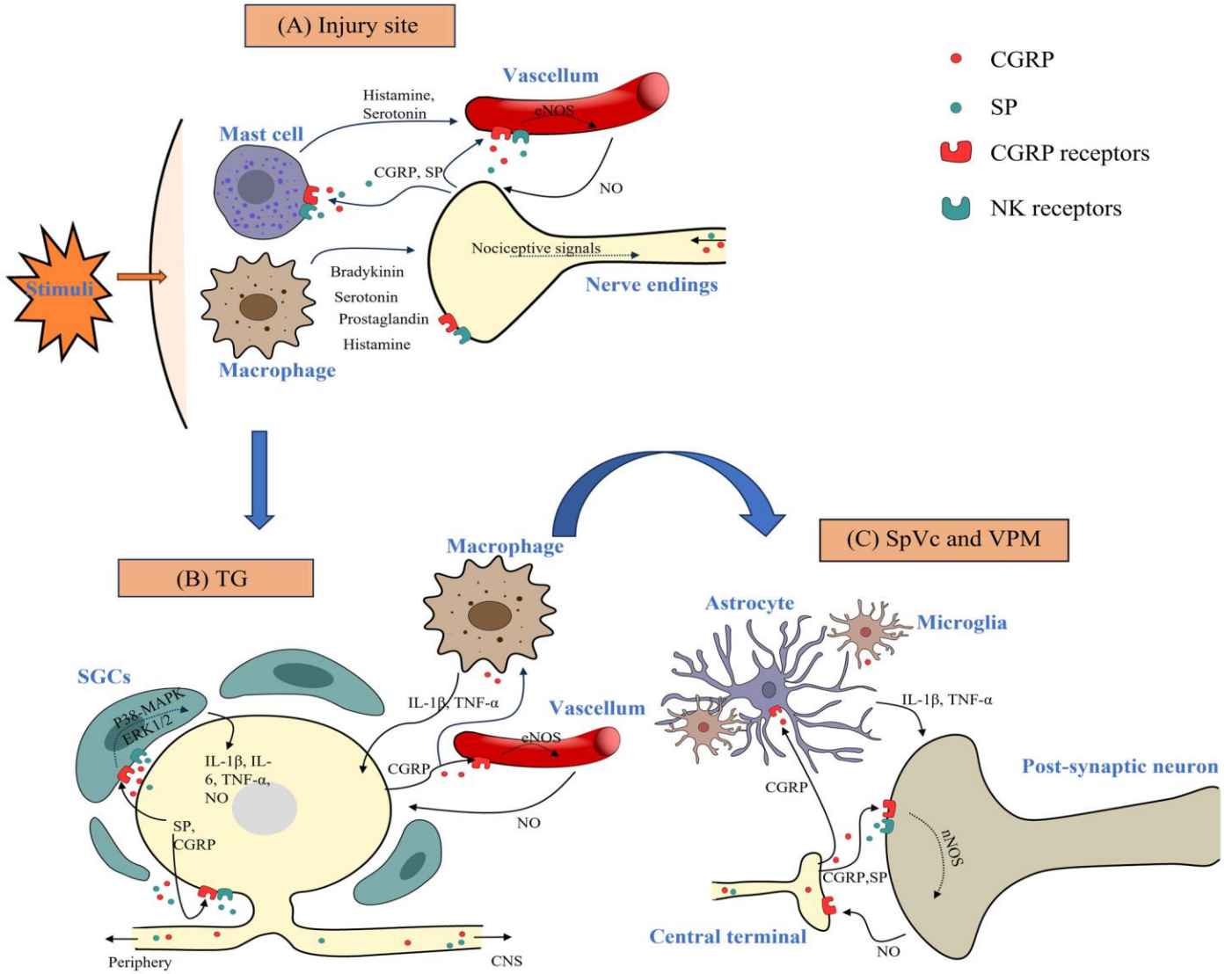


Kim YK, Granstein RD, Roles of calcitonin gene-related peptide in the skin, and other physiological and pathophysiological functions,Brain, Behavior, & Immunity - Health, Volume 18,2021, 100361,ISSN 2666-3546, https://doi.org/10.1016/j.bbih.2021.100361.

CGRP Trigeminal nociception



Trigeminal Neuralgia: What It Is, Causes, Symptoms & Treatment



J of Oral Rehabilitation, Volume: 51, Issue: 5, Pages: 898-908, First published: 11 January 2024, DOI: (10.1111/joor.13656)

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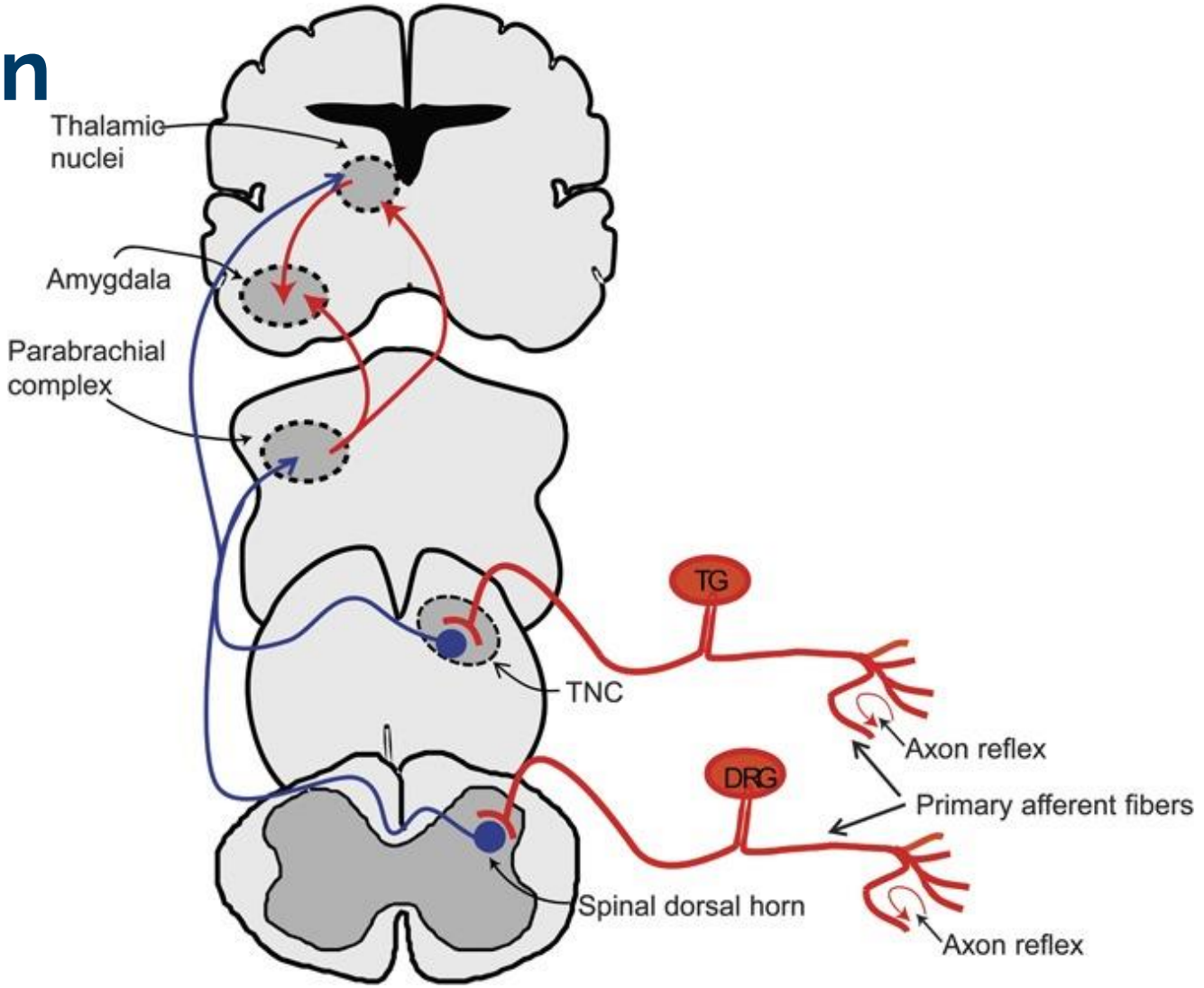
CGRP peripheral & central sensitisation

Activates and recruits immune cells	↑ Inflammatory cytokines
↑ Blood flow	Neurogenic inflammation
↑ NO synthesis	Amplification
Glial cell activation	Amplification and persistency
Upregulates receptors and ion channels	Enhanced neuronal excitability

Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017 Apr;158(4):543-559. doi: 10.1097/j.pain.0000000000000831. PMID: 28301400; PMCID: PMC5359791. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the Trigeminal System in Migraine. Headache. 2019 May;59(5):659-681. doi: 10.1111/head.13529. Epub 2019 Apr 14. PMID: 30982963; PMCID: PMC6593989.

CGRP expression



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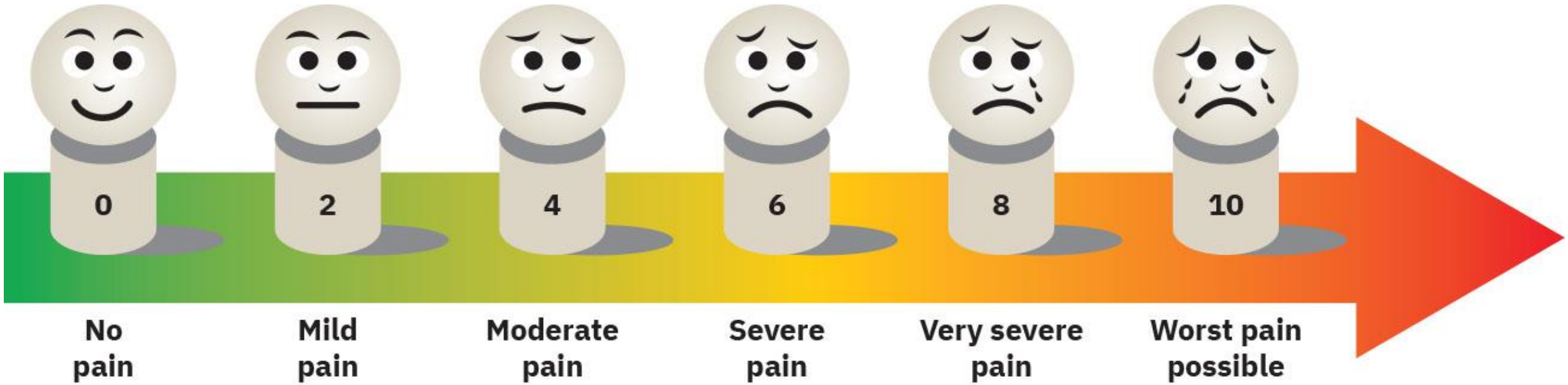

Image credit:16.2: Responses to Pain - Medicine LibreTexts

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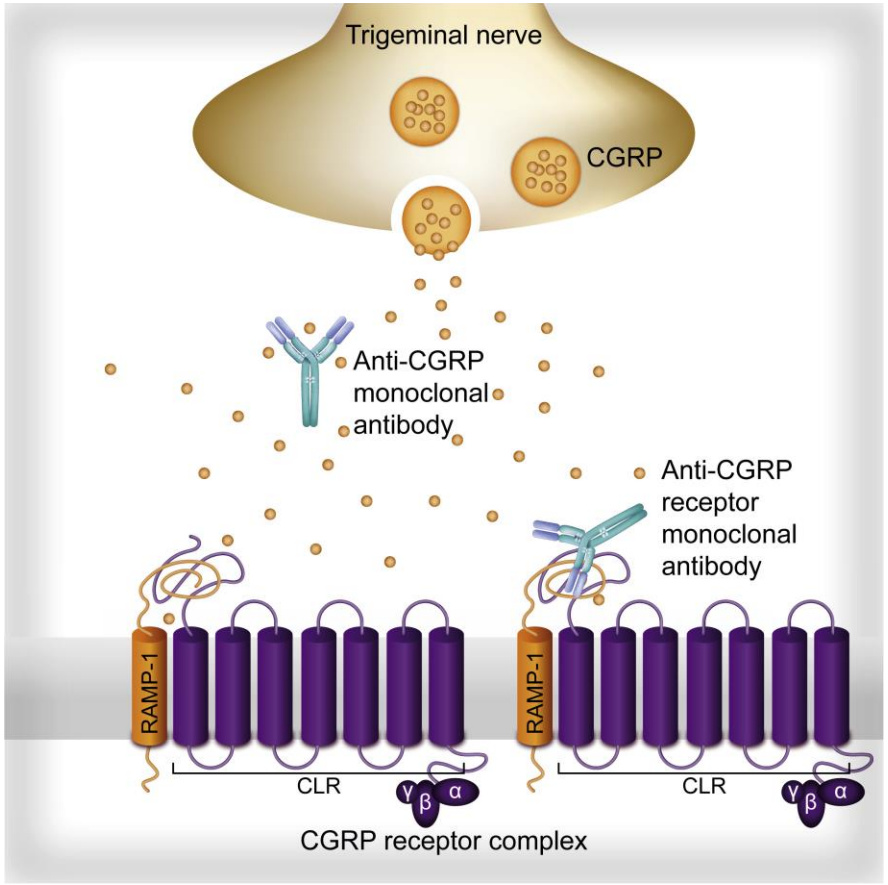
CGRP inhibitors

From Newcastle. For the world.

Monocolonal antibodies (MAb)



Maureen Moriarty, Theresa Mallick-Searle, Carol A. Barch, Kim Oas, Monoclonal Antibodies to CGRP or Its Receptor for Migraine Prevention, The Journal for Nurse Practitioners, Volume 15, Issue 10, 2019, Pages 717-724.e1, ISSN 1555-4155, https://doi.org/10.1016/j.nurpra.2019.07.009.

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CGRP Mabs

Drug	Target	Route	Dose
Erenumab	Receptor	SC	70 or 140mg monthly
Eptinezumab	Ligand	IV	100 mg or 300 mg 3/12M
Fremanezumab		SC	225mg monthly or 675mg 3/12M
Galcanezumab		SC	240 mg loading dose Then 120 mg monthly

Migraine Rationale

Migraine attack - ↑ CGRP peripheral and cranial circulation

CGRP infusion → migraine-like headache

CGRP induced meningeal and cerebral artery vasodilation

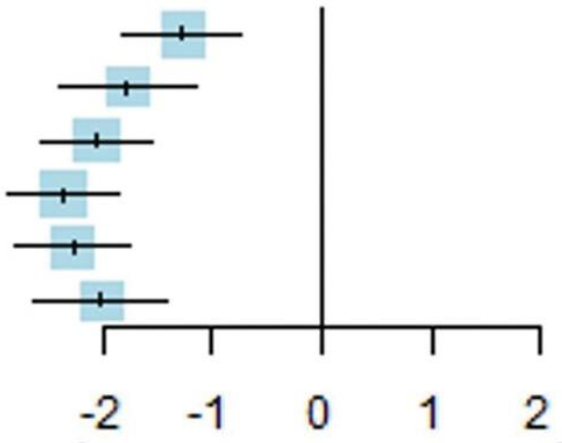
Neurogenic inflammation

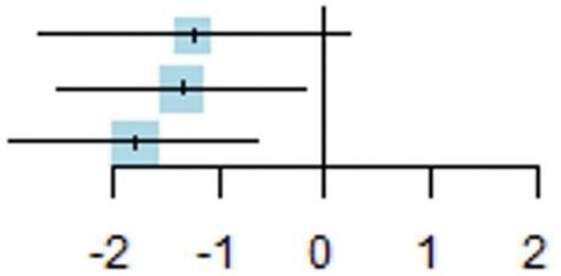
Sensitisation

Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets. 2020 Feb;24(2):91-100. doi: 10.1080/14728222.2020.1724285. Epub 2020 Feb 13. PMID: 32003253; PMCID: PMC7050542.

Monthly migraine days

	Treatment N	Placebo N	Comparison: other vs 'Placebo' (Random Effects Model)	Trials	MD	95%-CI
Subcutaneous administration						
Erenumab 70 mg	846	859		4	-1.27	[-1.81; -0.74]
Erenumab 140 mg	516	563		3	-1.78	[-2.41; -1.14]
Fremanezumab 225 mg	1240	1231		5	-2.06	[-2.57; -1.54]
Fremanezumab 675 mg	1242	1231		5	-2.36	[-2.87; -1.84]
Galcanezumab 120 mg	946	1654		4	-2.28	[-2.82; -1.74]
Galcanezumab 240 mg	705	1424		3	-2.02	[-2.63; -1.41]
Intravenous administration						
Eptinezumab 30 mg	223	222		1	-1.25	[-2.71; 0.21]
Eptinezumab 100 mg	577	588		2	-1.35	[-2.51; -0.19]
Eptinezumab 300 mg	572	588		2	-1.80	[-2.96; -0.63]





Haghdoost F, Puledda F, Garcia-Azorin D, Huessler E-M, Messina R, Pozo-Rosich P. Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: A systematic review and network meta-analysis of phase 3 randomised controlled trials. *Cephalalgia*. 2023;43(4). doi:10.1177/03331024231159366

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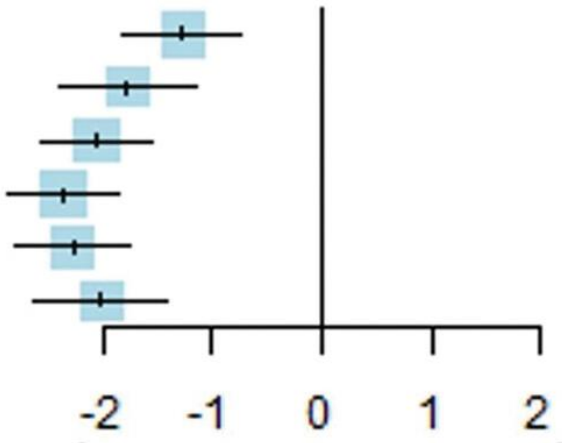

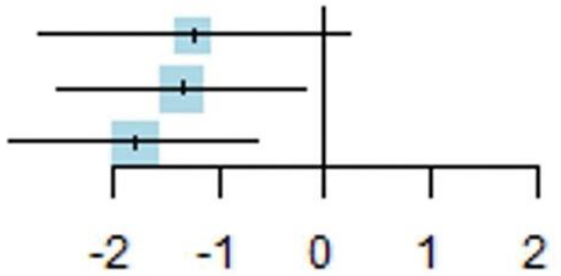

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≥50% Responder rate

	Treatment N	Treatment Events %	Placebo N	Placebo Events %	Trials	OR	95%-CI
Subcutaneous administration							
Erenumab 70 mg	846	42	859	29	4	1.83	[1.45; 2.30]
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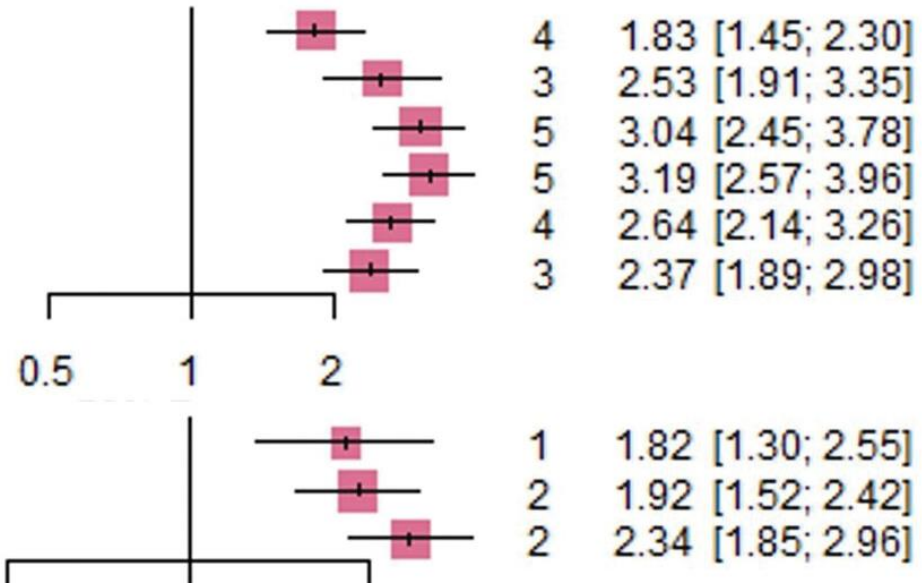
Fremanezumab 675 mg	1242	39	1231	17	5	3.19	[2.57; 3.96]
Galcanezumab 120 mg	946	46	1654	27	4	2.64	[2.14; 3.26]
Galcanezumab 240 mg	705	47	1424	29	3	2.37	[1.89; 2.98]
Intravenous administration							
Eptinezumab 30 mg	223	50	222	37	1	1.82	[1.30; 2.55]
Eptinezumab 100 mg	577	55	588	39	2	1.92	[1.52; 2.42]
Eptinezumab 300 mg	572	59	588	39	2	2.34	[1.85; 2.96]



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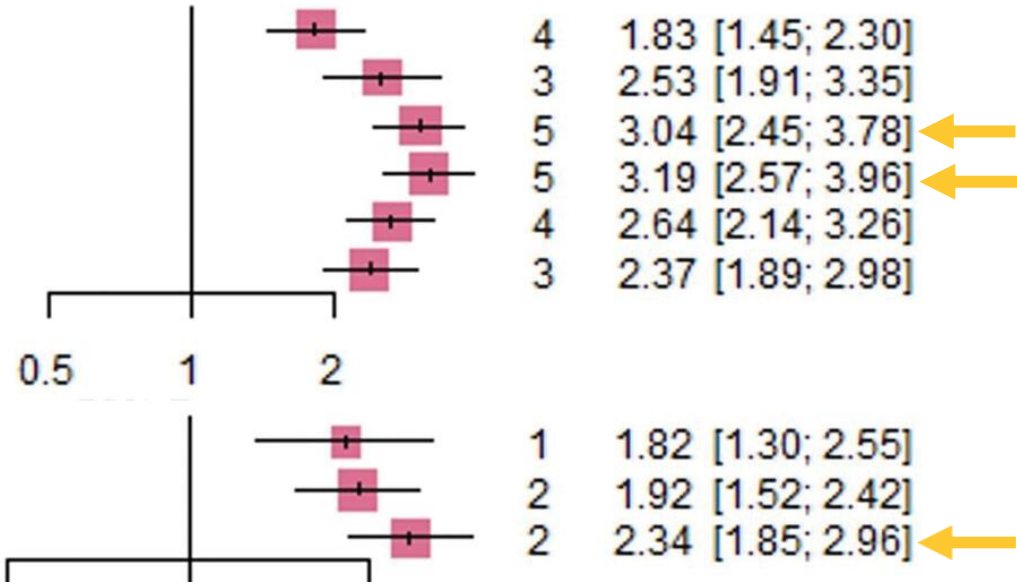

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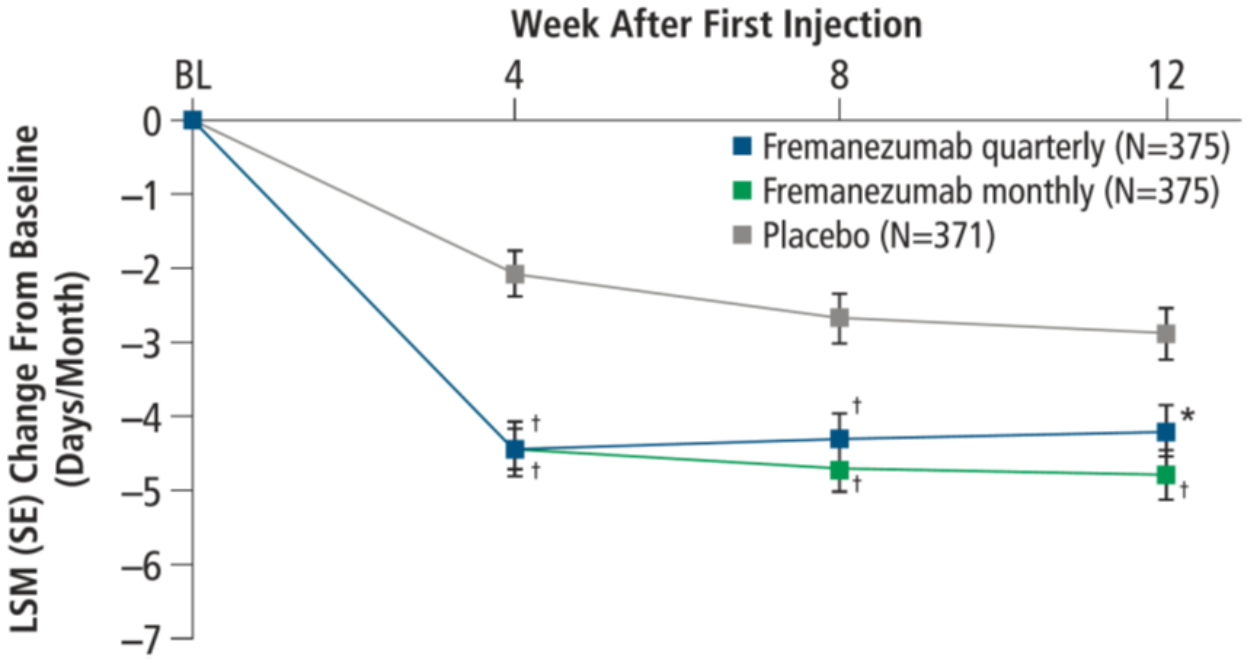
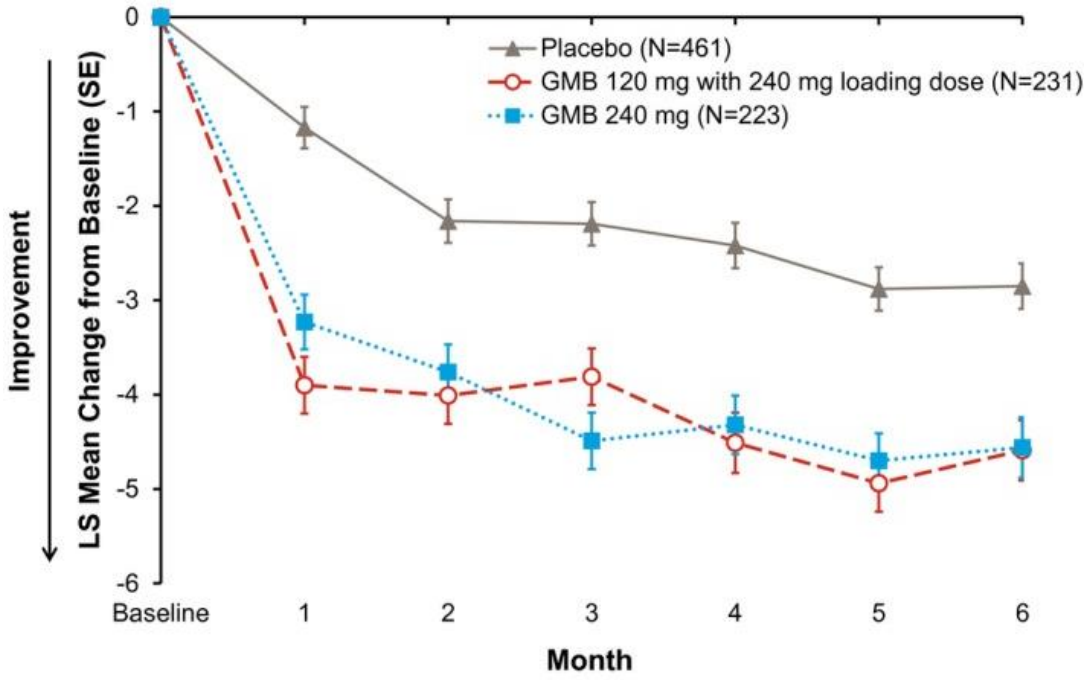
Onset of action





Brandes J *et al*. Poster P4.102. Presented at the American Academy of Neurology Annual Meeting, Los Angeles, CA, USA. 2018
Detke HC,et al. Rapid Onset of Effect of Galcanezumab for the Prevention of Episodic Migraine: Analysis of the EVOLVE Studies. Headache. 2020 Feb;60(2):348-359. doi: 10.1111/head.13691. Epub 2019 Nov 11. PMID: 31710104; PMCID: PMC7028148.

European Headache federation 2022 and American Headache Society 2024

First line for migraine prevention

"Initiation of these therapies should not require trial and failure of other migraine preventive medications"

Sacco S *et al.* European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022 Jun 11;23(1):67. doi: 10.1186/s10194-022-01431-x. PMID: 35690723; PMCID: PMC9188162.
Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024; 64: 333-341. doi:**10.1111/head.14692**

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CGRP for TMD

From Newcastle. For the world.

CGRP for TMD: Rationale

CGRP expressed in TMJ, MOM

Key role in neuroinflammation and sensitisation

~~Biomarker~~

Animal models

↑ CGRP concentrations in TMJ and MOM tissue

↑ CGRP-expressing neurons

↓ Pain behaviours

Tchivileva IE, et al. Evaluation of Plasma Calcitonin Gene-Related Peptide as a Biomarker for Painful Temporomandibular Disorder and Migraine. *J Pain Res*. 2023;16:2331-2346. https://doi.org/10.2147/JPR.S408044. Carleson J, Lundeberg T, Appelgren B (2001). "Bilateral increases of Calcitonin gene-related peptide in experimentally induced unilateral rat masseter myositis." J Orofac Pain Carleson J, Bileviciute I, Theodorsson E, Appelgren B, Appelgren A, Yousef N, Kopp S, Lundeberg T. Effects of adjuvant on neuropeptide-like immunoreactivity in the temporomandibular joint and trigeminal ganglia. J Orofac Pain. 1997 Summer;11(3):195-9. PMID: 9610308.

TMD: Evidence to date

~~Published RCTs~~

Registered 1 terminated 2024

Newcastle University

CGRP for TN

From Newcastle. For the world.

CGRP for TN: Rationale

Human

↑ CGRP levels (Serum and CSF)

Animal

↑ CGRP in TgG

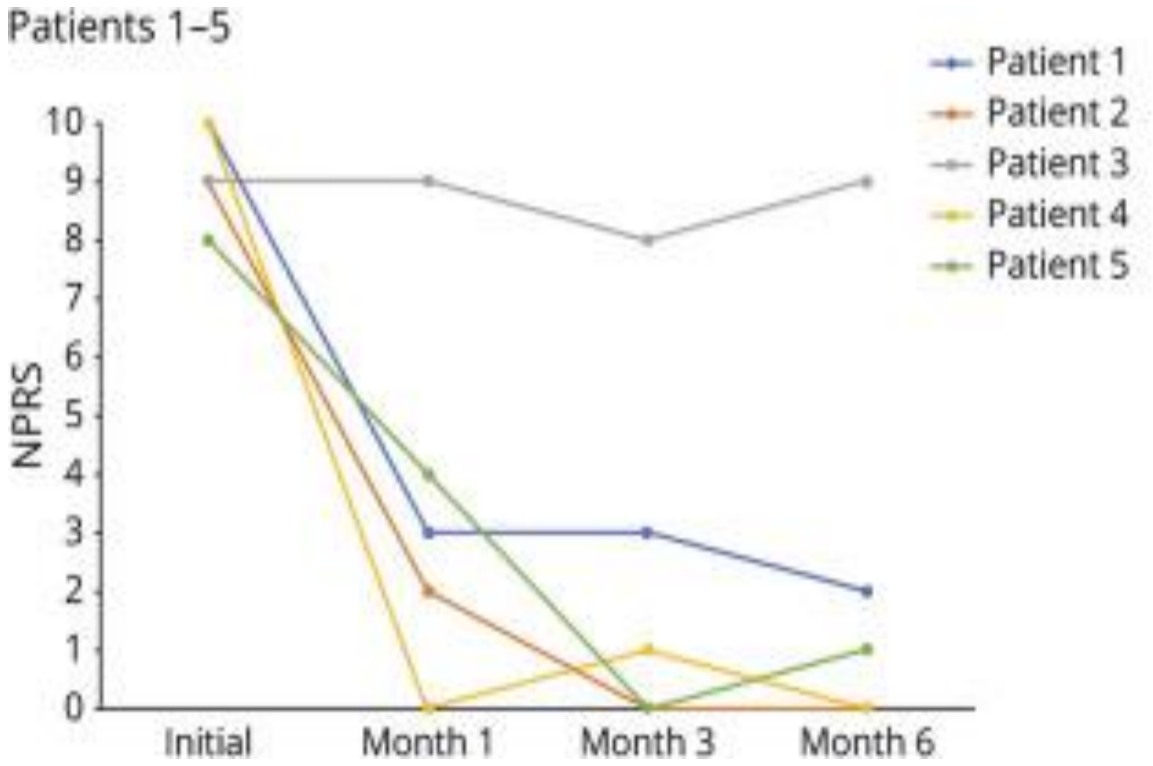
CGRP Mab = ↓ pain behaviour

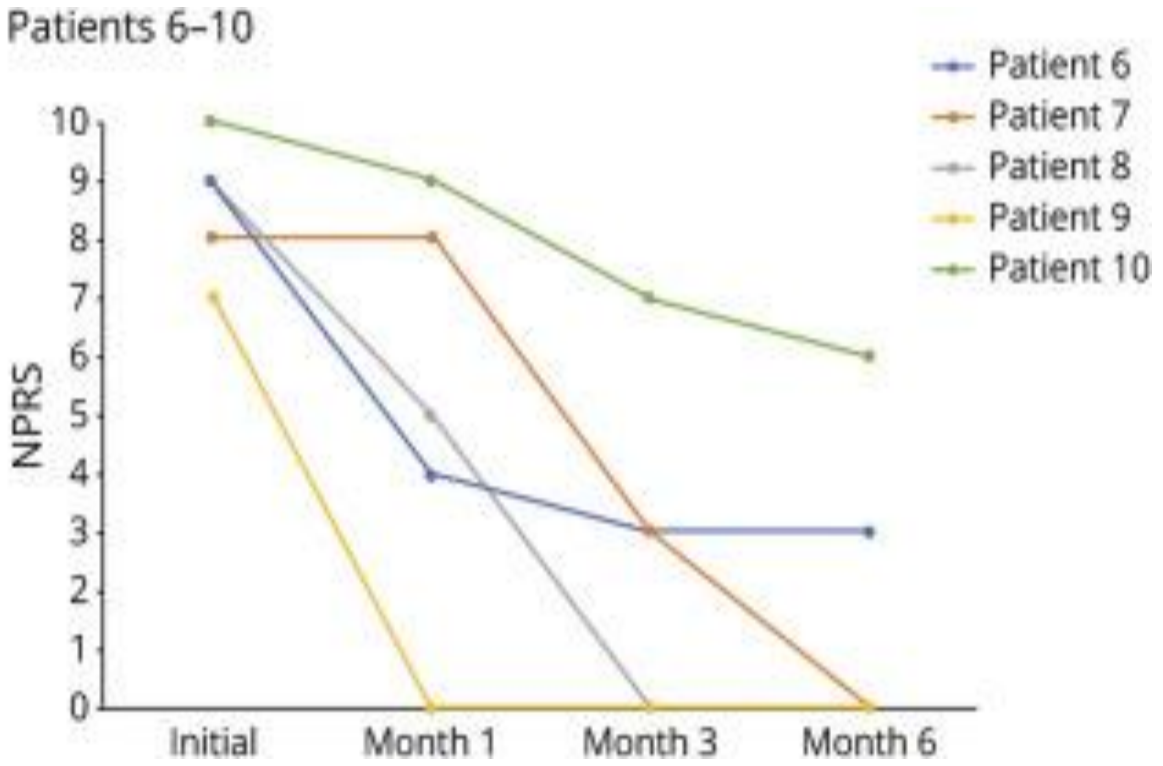
Farajzadeh A, Bathaie SZ, Arabkheradmand J, et al. Different pain states of trigeminal neuralgia make significant changes in the plasma proteome and some biochemical parameters: a preliminary cohort study. J Mol Neurosci 2018;66:524-534. Qin Z, Yang L, Li N, et al. Clinical study of cerebrospinal fluid neuropeptides in patients with primary trigeminal neuralgia. Clin Neurosurg 2016;143:111-115.

CGRP for TN clinical evidence

Study	Patient	Intervention	Comparator	Comments
Parascandolo *et al* 2021	Refractory TN (ICHD-3) N=10 (7f:3m) ? Branches	Erenumab Dose ? 6/12M	Nil	Case series Constipation (n=2) Injection site reaction (n=2)

Parascandolo E, Levinson K, Rizzoli P, Sharon R. Efficacy of Erenumab in the Treatment of Trigeminal Neuralgia: A Retrospective Case Series. Neurol Clin Pract. 2021 Jun;11(3):227-231. doi: 10.1212/CPJ.0000000000001075. PMID: 34484889; PMCID: PMC8382339.





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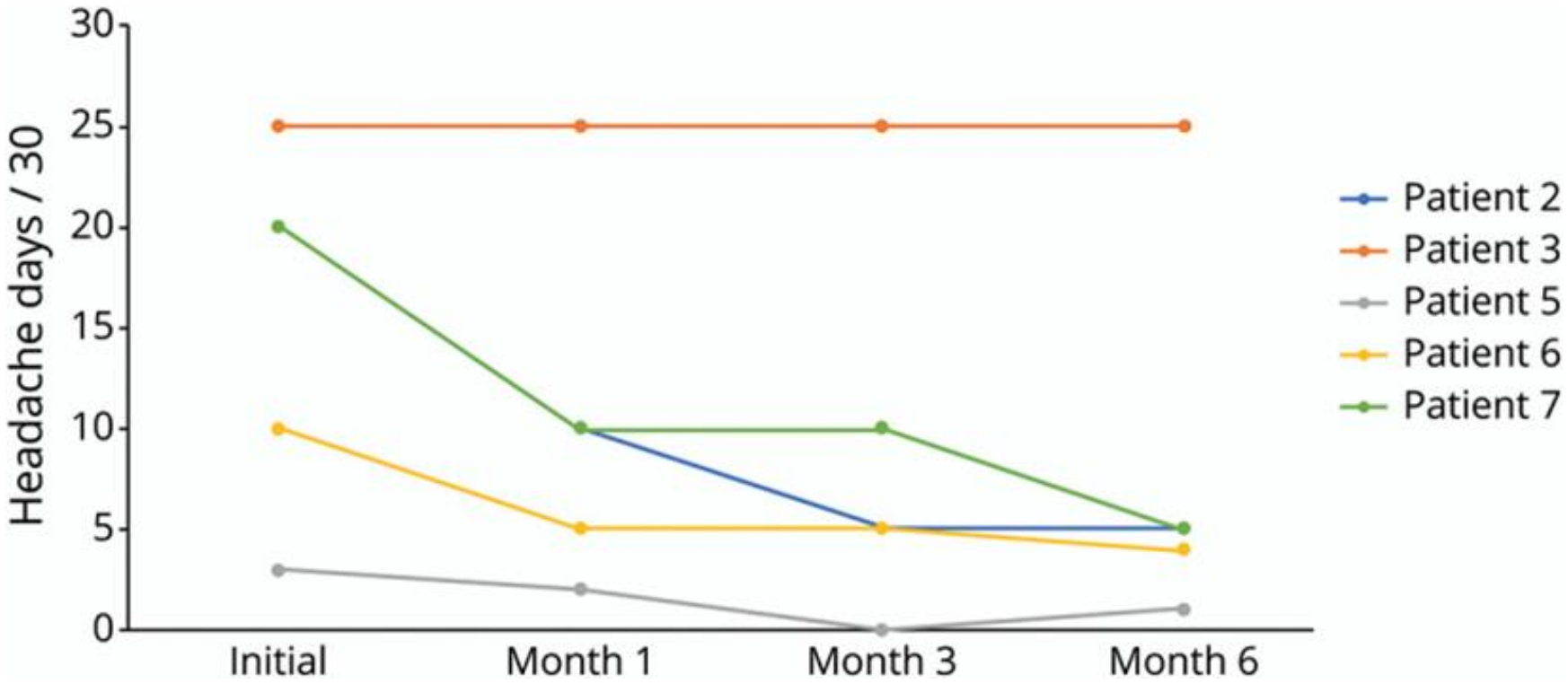
TN + comorbid migraine



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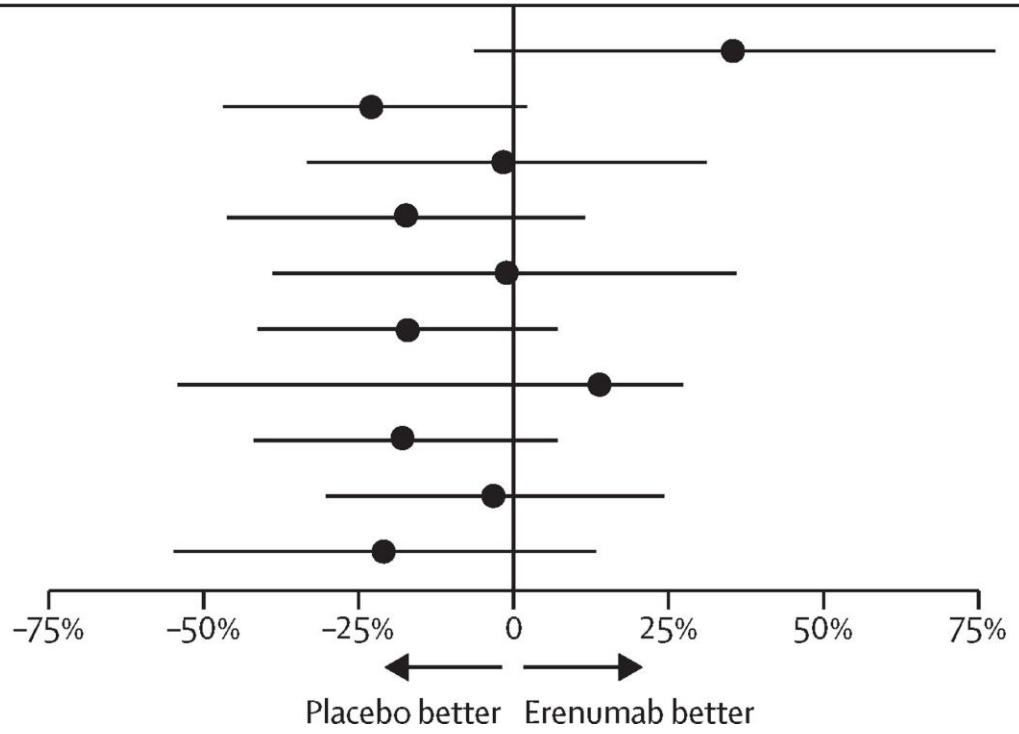
Study	Patient	Intervention	Comparator	Comments
Schott Anderse, AS *et al*. 2022	Idiopathic or classic TN (ICHD-3) (n=40) V1 3% V2 23% V3 8% V1+V2 5% V2+V3 45% V1, V2, V3 23%	Erenumab 140mg SC	Placebo (n=40)	RCT double blind, placebo-controlled **Erenumab group** Constipation (28%) Headache (10%) **Placebo group** Headache (13%), Constipation (10%) Abdominal pain (10%)

Schott Andersen, Anne Sofie et al. Safety and efficacy of erenumab in patients with trigeminal neuralgia in Denmark: a double-blind, randomised, placebo-controlled, proof-of-concept study.The Lancet Neurology, Volume 21, Issue 11, 994 - 1003

	Placebo (n=40)	Erenumab (n=40)	Estimated treatment difference (95% CI)
Primary outcome			
≥30% reduction in mean average daily pain intensity score (intention-to-treat analysis)	18 (45%)	14 (35%)	−10% (−31 to 11); p=0·36

	Number of responders		Estimated treatment difference (95% CI)
	Placebo	Erenumab	
Purely paroxysmal pain	5/14 (36%)	5/7 (71%)	36% (−6 to 78)
Concomitant continuous pain	13/26 (50%)	9/33(27%)	−23% (−47 to 2)
Classical trigeminal neuralgia	8/19 (42%)	7/17 (41%)	−1% (−33 to 31)
Idiopathic trigeminal neuralgia	10/21 (48%)	7/23 (30%)	−17% (−46 to 11)
Mean average daily pain intensity ≥7	2/11 (18%)	1/6 (17%)	−2% (−39 to 36)
Mean average daily pain intensity <7	16/29 (55%)	13/34 (38%)	−17% (−41 to 7)
Male	6/13 (46%)	6/10 (60%)	14% (−54 to 27)
Female	12/27 (44%)	8/30 (27%)	−18% (−42 to 7)
Disease duration ≥5 years	11/26 (42%)	9/23 (39%)	−3% (−30 to 24)
Disease duration <5 years	7/14 (50%)	5/17 (29%)	−21% (−55 to 13)



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CGRP TN and other trigeminal NP

Study	Patient	Intervention	Comparator	Comments
Lee *et al.* 2020	N=23 65% TN 9% Post traumatic trigeminal neuropathy 26% Atypical facial pain 70% comorbid migraine 4% comorbid cluster headache	Erenumab (65%) Fremanezumab (22%) Galcanezumab (13%)	Nil	Case series ≈ 50% improvement 4.8m av. therapy

Case examples

Male 7th decade

Severe dull throbbing ache right maxilla, right zygoma

- Familiar pain right masseter

Intermittent severe exacerbations "*stabbing tightness*"

- No obvious trigger zone

Intermittent paraesthesia right V2

- Short lived
- Only present when pain at its worse

TMD: Initial Management

- Splint
- TMD supported self-management
- Gabapentin

Further investigations:

- Bloods
- MRI head

Review

- Pain on palpation of masseter improved ++
- No improvement in complaint
- Vascular contact on MRI

Review

- Pain on palpation of masseter improved ++
- No improvement in complaint
- Vascular contact on MRI

Witnessed attack

- Severe ++
- Facial spasm
- Refractory period

1. Classical TN with concomitant background pain (V2)

2. M-TMD (2°)

- CBZ
  - Positive initial response (short lasting)
  - 1600mg pain <20% improved
- MVD
  - Positive <3months

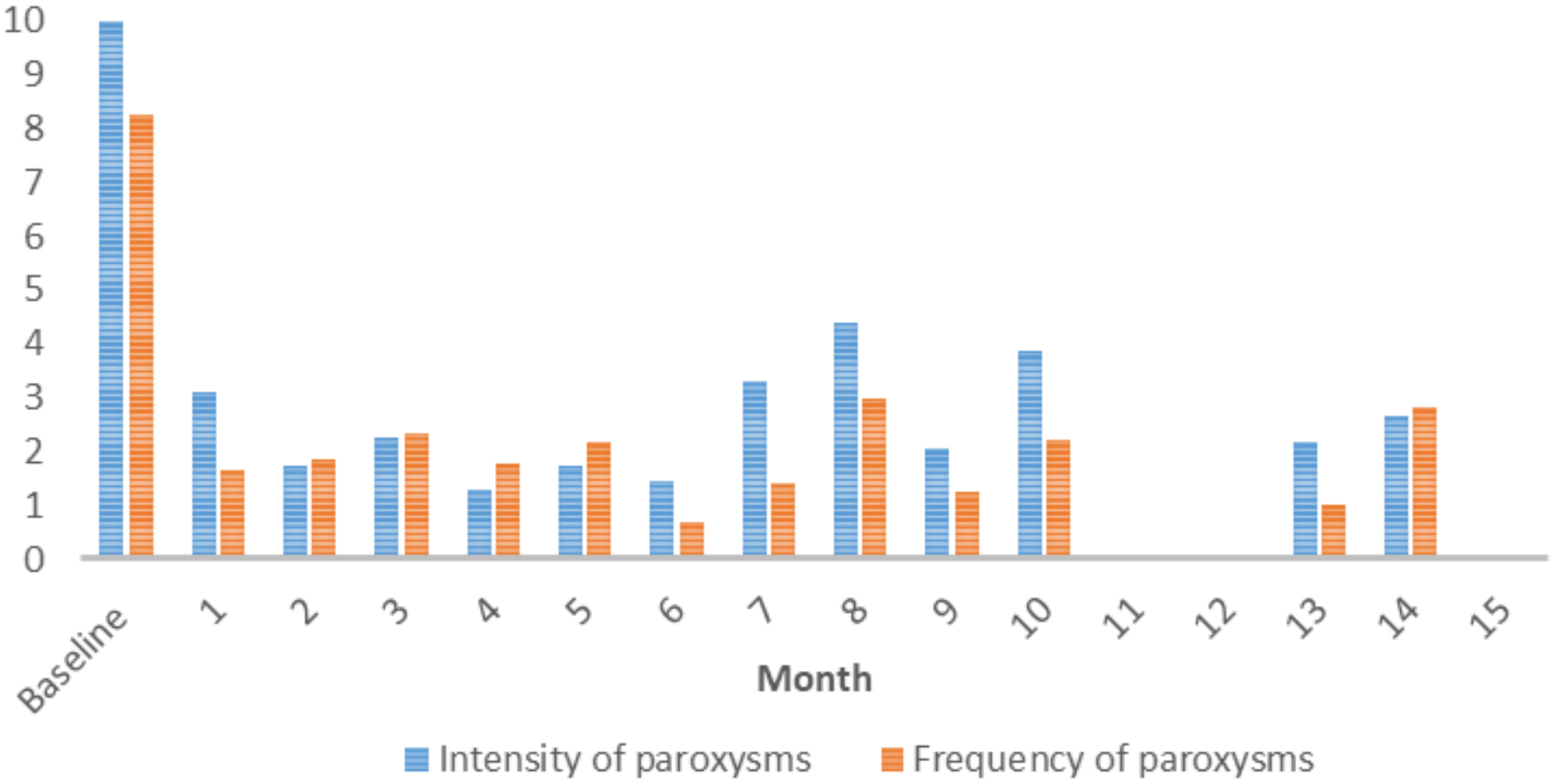
- OXC
- CBZ + Gabapentin
- CBZ + Pregabalin
- Sustained release CBZ
- CBZ + lamotrigine
- Botox V2
    - positive response
    - Initially ≈70% pain reduction
    - Response for 18 m

Fremenezumab 675mg SC three monthly

Justification:

- TN and TMD – CGRP implicated in pathogenesis of both conditions
- Refractory case
- Impact ++
- ? Other options

Treatment response



Female 6th decade

- Right sided idiopathic trigeminal neuralgia V1
- M-TMD
- Fibromyalgia
- Anxiety and Depression

Tolerated combination

- CBZ sustained release 900mg (400mg am, 100mg lunch, 400mg pm)
- Pregabalin 100mg TDS

Other

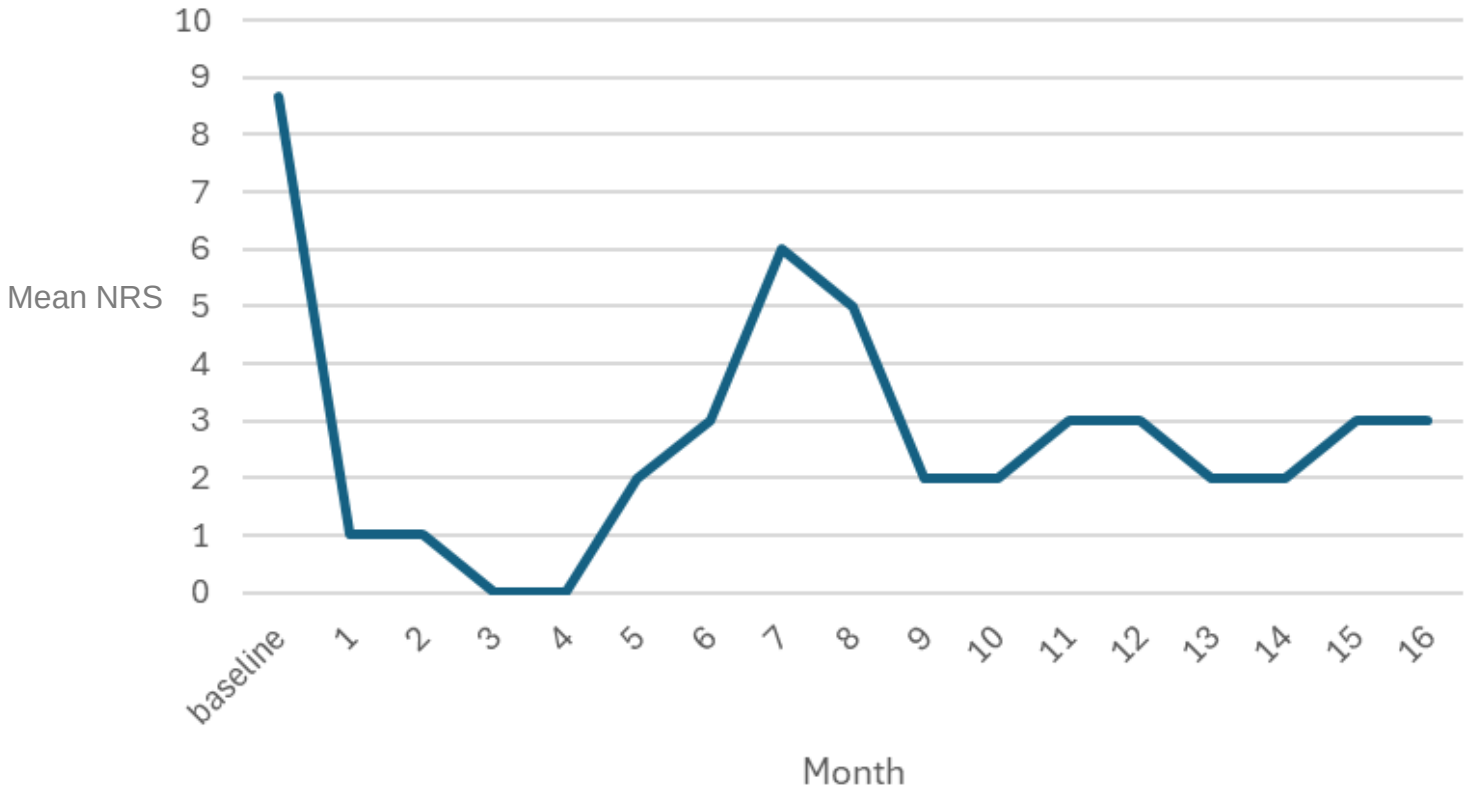
OXC, gabapentin, lidocaine patches, lamotrigine

~~Neurosurgical options~~

Baseline

Measure	Baseline	After 5 months of extensive evidenced-based medical management
Pain intensity	9.66	8.67
Pain related disability	10	9.66
PHQ-4	11	9

Treatment response



Summary

- Positive effect
- Not curative
- Adjuvant treatment
- No AEs

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Clinical considerations

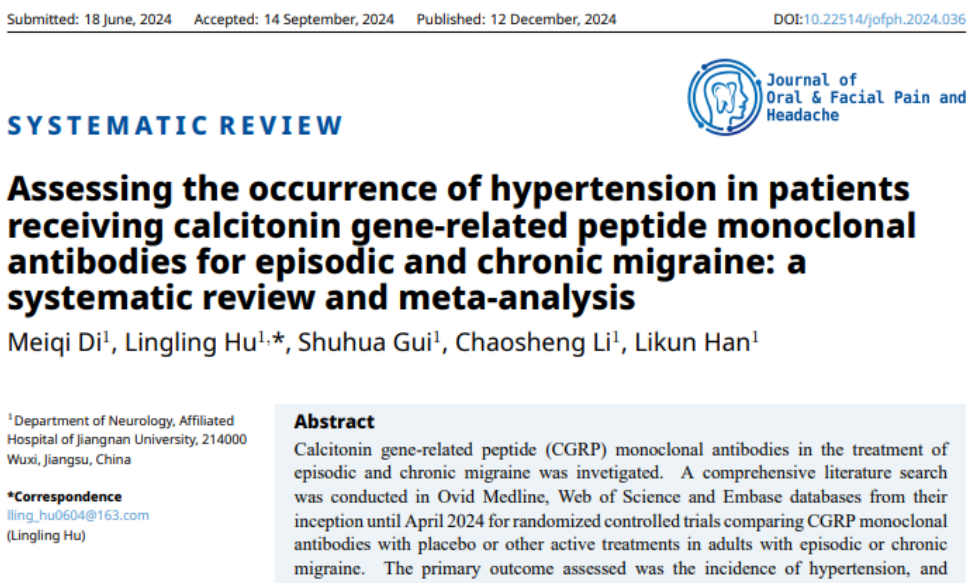
From Newcastle. For the world.

Mabs AEs

Adverse event	Prevalence range (%)	Implicated Mab
Injection site reaction	13-24	All
Fatigue	13	All, Eptinezumab+
Constipation	7-18	All, Erenumab+++
Cardiovascular (Serious)	1.5-1.6	All

Di M, Hu L, Gui S, Li C, Han L. Assessing the occurrence of hypertension in patients receiving calcitonin gene-related peptide monoclonal antibodies for episodic and chronic migraine: a systematic review and meta-analysis. J Oral Facial Pain Headache. 2024 Dec;38(4):24-32. doi: 10.22514/jofph.2024.036. Epub 2024 Dec 12. PMID: 39800953; PMCID: PMC11810671.

CV risk



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SYSTEMATIC REVIEW

Assessing the occurrence of hypertension in patients receiving calcitonin gene-related peptide monoclonal antibodies for episodic and chronic migraine: a systematic review and meta-analysis

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Abstract

Calcitonin gene-related peptide (CGRP) monoclonal antibodies in the treatment of episodic and chronic migraine was invetigated. A comprehensive literature search was conducted in Ovid Medline, Web of Science and Embase databases from their inception until April 2024 for randomized controlled trials comparing CGRP monoclonal antibodies with placebo or other active treatments in adults with episodic or chronic migraine. The primary outcome assessed was the incidence of hypertension, and

- Vascular events ?
- No significant increase in hypertension risk
- Individual risk assessment

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Absolute contraindications

- Hypersensitivity
- Pregnancy and breastfeeding
- Active or recent significant cardiovascular disease
  - Recent MI, stroke or TIA
  - Unstable cerebrovascular disease
  - Severe or unstable coronary artery disease, cardiomyopathy, or pulmonary hypertension.
  - Uncontrolled or severe hypertension (until controlled).
- Severe constipation

Sacco S et al . European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022 Jun 11;23(1):67. doi: 10.1186/s10194-022-01431-x. PMID: 35690723; PMCID: PMC9188162.

Caution

- Stable, well-managed CV disease
- Mild/intermittent constipation
- Raynaud's

Newcastle University

Sensible current conclusions

- Well tolerated
- Sensible science
- No guarantee
- Refractory cases
- Multiple trigeminal pain conditions (esp. if migraine)
- V1>V2>V3

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