

UPDATE ON HEADACHE TREATMENT

Newly Approved, Emerging, and Alternative Therapies

Stacy V. Smith, MD

Houston Methodist Neurological Institute, Blanton Eye Institute, Weill Cornell
Medicine

Assistant Professor of Clinical Neurology

- Speaker Bureau
 - *Eli Lilly (2022)**
 - *Biohaven Pharmaceuticals (2022)**
- Consultant
 - American Medical Response: Motorsports Neurology Consultant

**All discussion will be per the FDA label for these products, and all similar agents from the relevant drug classes are included*

- New and Emerging Medications
- Neuromodulation: Headache Devices
- Complementary Therapies
- Role for the Ophthalmologist and Anesthesiologist

- Subcutaneous Injection
 - Erenumab-aooe ($T_{1/2}$ 28d)
 - 70 or 140 mg monthly
 - Galcanezumab-gnlm ($T_{1/2}$ 27d)
 - 240 mg loading dose, then 120 mg monthly
 - *Episodic Cluster: 300 mg monthly
 - Fremanezumab-vfrm ($T_{1/2}$ 31d)
 - 225 mg monthly or 675 mg quarterly
- Intravenous Infusion
 - Eptinezumab-jjmr ($T_{1/2}$ 27d)
 - 100 mg or 300 mg quarterly

- Ubrogepant (PO)
 - 50 mg or 100 mg PRN, max 2/day
- Rimegepant (PO)
 - 75 mg PRN *or* 75 mg QOD, may 1/day
- Atogepant (PO)
 - 10 mg, 30 mg, or 60 mg daily
- Zavegepant (NS)
 - 10 mg PRN, max 1/day

ADDITIONAL ACUTE MEDICATIONS

- Ditans: 5-HT_{1F} serotonin receptor agonist
 - Lasmiditan (2019)
 - 50 mg, 100 mg, or 200 mg
 - Schedule V
- Ergots
 - Dihydroergotamine mesylate nasal spray (2021)
 - “precision olfactory delivery” device
- COX2 Inhibitors
 - Celecoxib oral solution (2021)

ONGOING DEVELOPMENT

- New routes/formulations of existing agents
 - Gepant nasal spray (2023)
 - DHE precision olfactory delivery, dry nasal powder
 - Sumatriptan nasal spray, enhanced permeability
 - AXS 07: Rizatriptan and meloxicam combination agent
 - ABP-450: prabotulinumtoxinA
- New Indications for existing medications
 - Cluster headaches
 - Galcanezumab, Erenumab, Eptinezumab
 - Rimegepant, SPG stimulator
 - Hemicrania Continua
 - Erenumab
 - Post-Traumatic Headaches
 - Fremanezumab
 - Gabapentin for SAH patients
- New Patient Populations
 - Pediatric and Adolescent

EMERGING TARGETS¹⁻⁷

- Pituitary Adenylate Cyclase Activating Peptide (PACAP38)
 - PAC1 receptor mAB: **AMG 301**
 - PACAP38 mAB: Lu AG09222, **LY3451838**
 - PACAP38 and PACAP27 mAB: ALD 1910
- Orexin
 - **Filorexant**
- Oxytocin
 - TNX-1900 (Intranasal, for CM prevention)
- Growth Hormone Receptor
 - LAT-8881

EMERGING TARGETS¹⁻⁷

- Histamine Receptor Modulation
 - Histamine Receptor Modulation: AGX-201
 - H1 antagonist: **clemastine**
- Nitric Oxide Synthase
 - iNOS inhibitors: **GW274150, NXN-188, NXN-413**
- Metabotropic glutamate receptor 5 (mGluR5)
 - **Raseglurant/ADX10059** (effective for acute migraine, but caused hepatotoxicity)
- Delta Opioid Receptor
 - δ agonist: **TRV 250 (phase 1)**

FUTURE TARGETS⁶⁻⁷

- Kappa Opioid Receptor
- VIP
- Amylin
- Adrenomedullin
- Phosphodiesterase
 - PDE3
 - PDE5
- kATP
- Potassium and Calcium Channels
- Purinergic System
- Transient Receptor Potential (TRP) Channel
- Glutamate

NEUROMODULATION⁸

- Hand-held vagal nerve stimulator
- Nerve stimulation
 - occipital and supraorbital
- Transcranial magnetic stimulation
- Remote electrical stimulation



INVASIVE OPTIONS⁹

For the treatment-refractive patient

- Deep Brain Stimulator
 - Posterior hypothalamic area for chronic cluster headache
- Occipital Nerve Stimulator
 - Chronic migraine and cluster headache
- Sphenopalatine Ganglion Stimulator
 - Maxillary mucosa

- Sprint PNS
 - Temporary implant, percutaneous, up to 60 days
- “Migraine Treatment System” PNS
 - Trial ongoing by Theranova
 - Stimulation of bicep
- Septal Occlusion
 - RELIEF trial
 - Transcatheter closure of patent foramen ovale (PFO)

- For photophobia/light sensitivity

- Evidence of benefit in

- Migraine
- Blepharospasm
- Chronic Ocular Pain
- Post-Concussion/Post-Traumatic Brain Injury



COMPLEMENTARY THERAPIES

- Acupuncture
- Cognitive Behavioral Therapy
- Biofeedback
- Hypnosis
- Wellness
- Exercise

- Peripheral nerve blocks
- Sphenopalatine ganglion block
- Radiofrequency nerve ablation
- Dry needling
- IV infusions
 - Magnesium
 - DHE
 - Lidocaine
 - Ketamine
 - Propofol

PERIPHERAL NERVE BLOCKS¹²

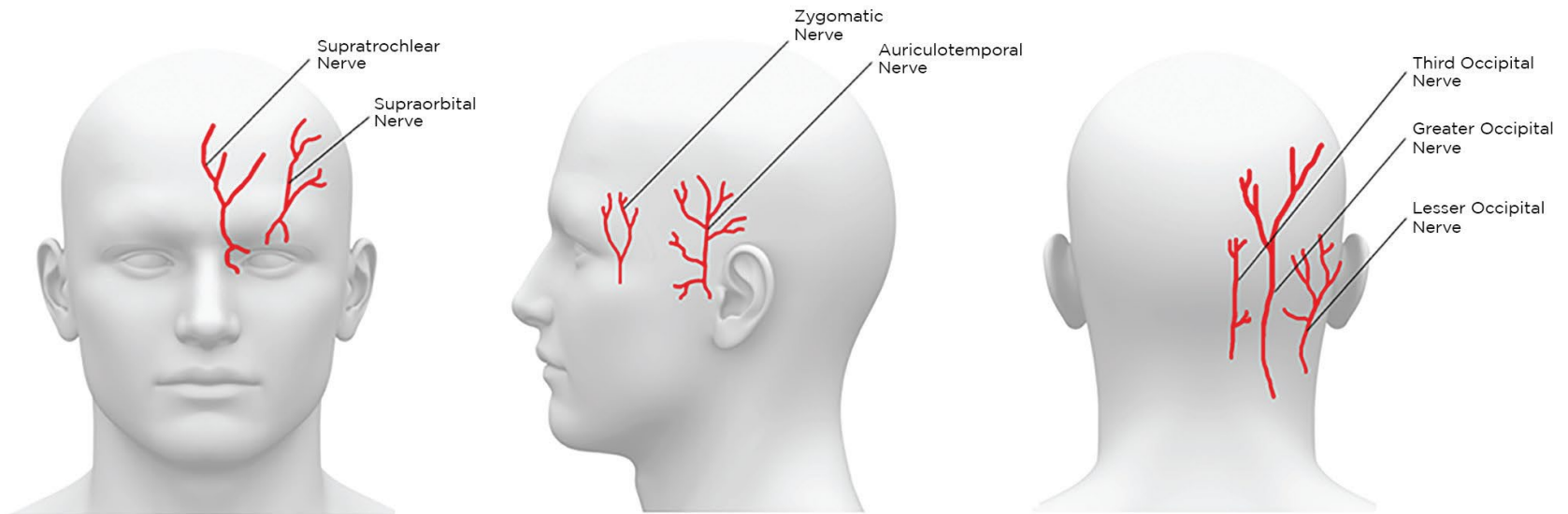


Image: Dias BDF, Frederico TN, Filho ID, Peres MFP. Full head block for headache treatment: technical description, indications and mechanisms. *Headache Medicine*. 2019;10(2):37-40.

- Role of the Ophthalmologist and Anesthesiologist
 - Recognize and refer
 - Management of the comorbid dry eye and photophobia
 - Interventions: infusions and blocks

REFERENCES

1. Ogunlaja O, Karsan N, Goadsby P. Emerging drugs for the prevention of migraine. *Expert Opinion on Emerging Drugs*. 2021;26(3):271-280.
2. Bertels Z, Pradhan AAA. Emerging treatment targets for migraine and other headaches. *Headache*. 2019;59(S2):50-65 .
3. Do TP, AL-Saoudi A, Ashina M. Future prophylactic treatments in migraine: Beyond anti-CGRP monoclonal antibodies and gepants. *Revue Neurologique*. 2021;111(7):827-833
4. Chaudhari K, Syed BA. The pipeline and market for migraine drugs. *Nature: From the Analyst's Couch*. 2023, November 17. Accessed January 8, 2024: <https://www.nature.com/articles/d41573-023-00182-x>.
5. Vollesen LH, Guo S, Andersen MR, Ashina M. Effect of the H1-antihistamine clemastine on PACAP38 induced Migraine. *Cephalalgia*. 2019;39(5):597-607.
6. Al-Hassany L, et al. Future targets for migraine treatment beyond CGRP. *The Journal of Headache and Pain*. 2023;24:76.
7. Silvestro M, et al. Migraine Treatment: Towards New Pharmacological Targets. *International Journal of Molecular Sciences*. 2023;24:12268.
8. Smith SV. Update on migraine: new understanding of pathophysiology and treatments. *American Academy of Ophthalmology Focal Points*. January 2020.
9. Cvetkovic VV, Jensen RH. Neurostimulation for the treatment of chronic migraine and cluster headache. *Acta Neurol Scand*. 2019;139:4-17.
10. Katz BJ, Digre KB. Diagnosis, pathophysiology, and treatment of photophobia. *Surv Ophthalmol*. 2016;61(4):466-477.
11. Reyes N, et al. FL-41 tint reduces activation of neural pathways of photophobia in patients with chronic ocular pain. *Am J Ophthalmol*. 2023, December 12 (online ahead of print).
12. Dias BDF, Frederico TN, Filho ID, Peres MFP. Full head block for headache treatment: technical description, indications and mechanisms. *Headache Medicine*. 2019;10(2):37-40.

HOUSTON
Methodist[®]
LEADING MEDICINE