Advances in Abortive Therapies in Migraine and Cluster Headache

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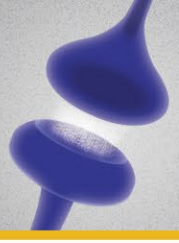
Disclosures

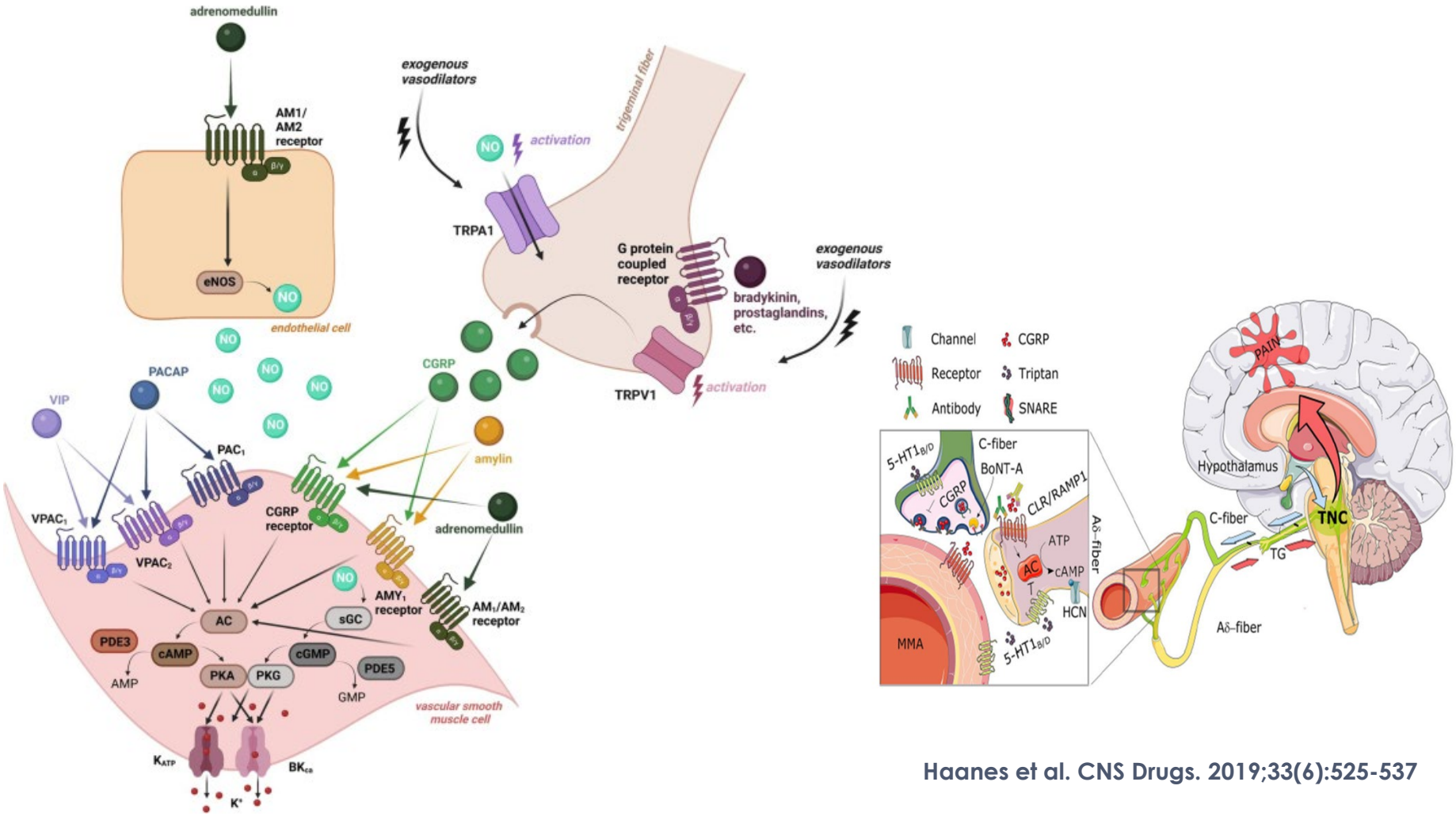
- Consultant, Advisor, Speaker
  - Abbvie/Allergan

Abortive Treatment of Migraine



- No longer “borrowing” drugs indicated for other conditions
- From non-specific analgesics to:
  - Triptans
  - Gepants
  - Ditan

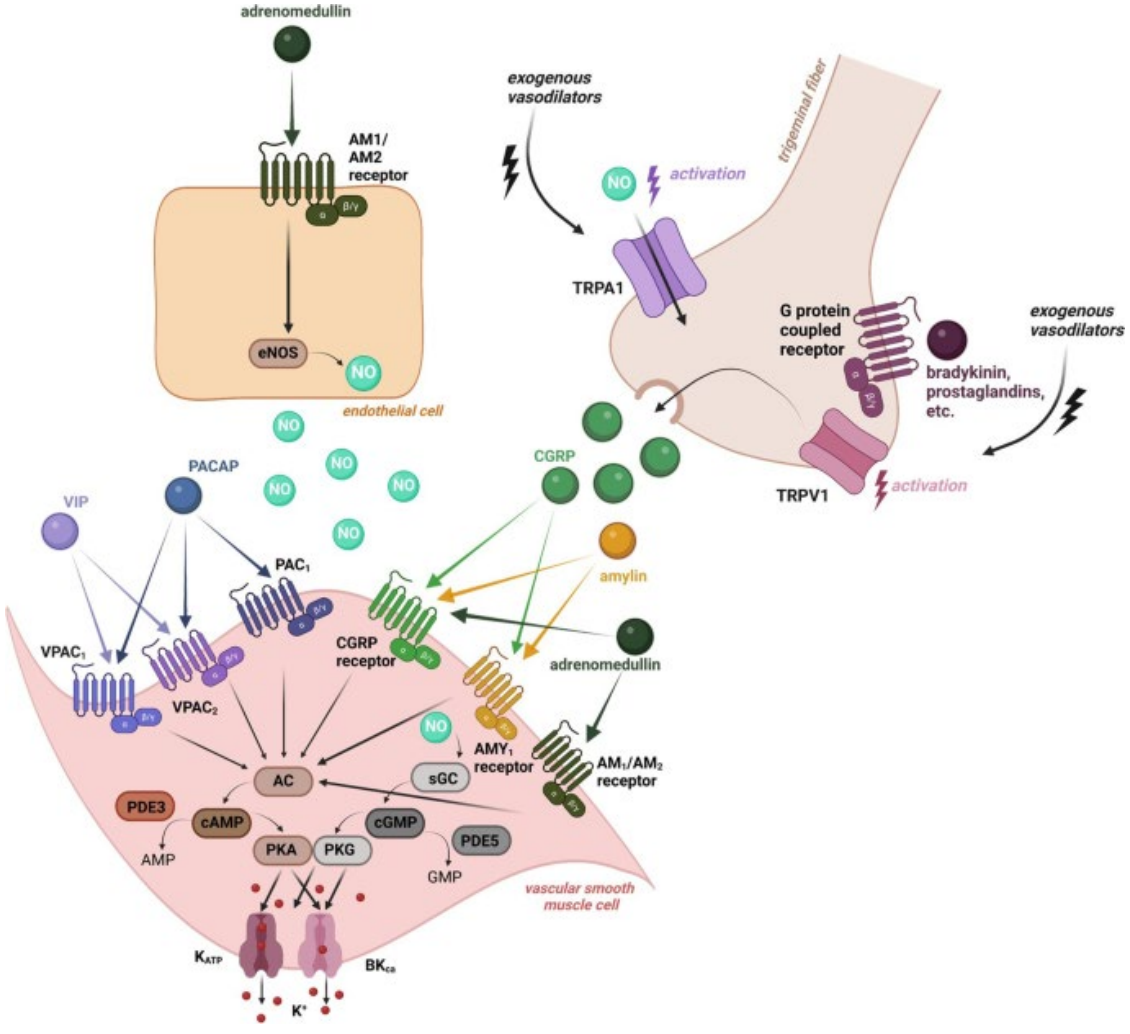
Migraine Mechanisms: Therapeutic Targets



Haanes et al. CNS Drugs. 2019;33(6):525-537

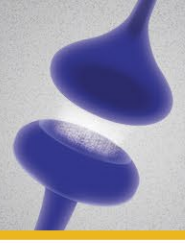
Al-Hassany et al. The Journal of Headache and Pain (2023) 24:76

Migraine Mechanisms: Therapeutic Targets



Al-Hassany et al. The Journal of Headache and Pain (2023) 24:76

Newer Therapies for acute Treatment

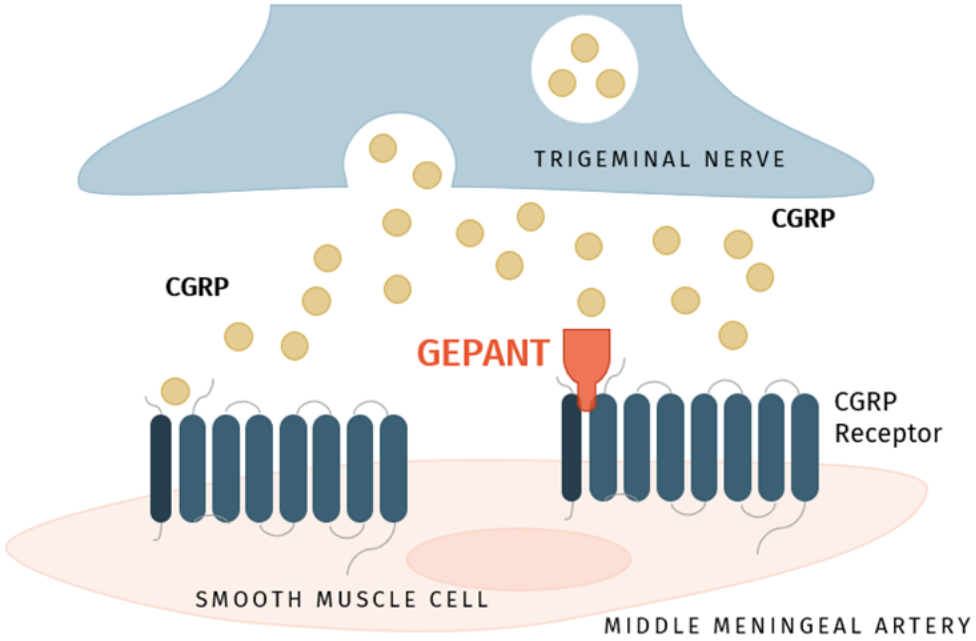


- Rimegepant (Nurtec)
- Ubrogepant (Ubrelvy)
- Zavegepant (Zavzpret)

- Lasmiditan (Reyvow)

Gepants

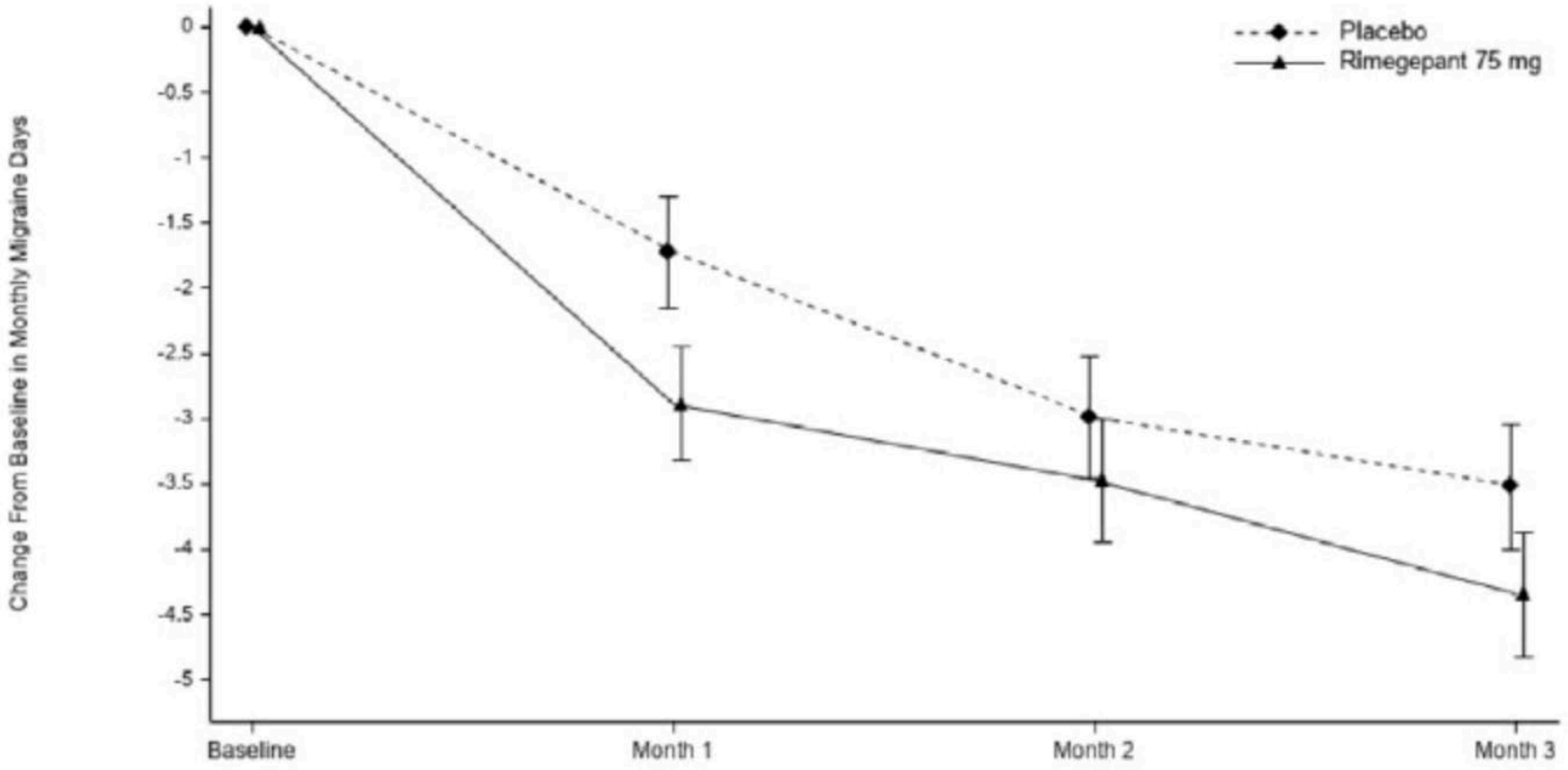
- Gepants bind to the same site on the CGRP receptor and block CGRP binding and receptor activation[1]
- Gepants have been approved for the acute treatment of migraine and preventive treatment of episodic migraine[2]:
  - No MOH warnings or precautions
  - No cardiovascular warnings or precautions
  - Not narcotics/not scheduled



1. Bell IM, J Med Chem, 2014. 2. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br J Clin Pharmacol. 2015. 3. Figure adapted from de Vries et al. Pharmacology & Therapeutics. 2020

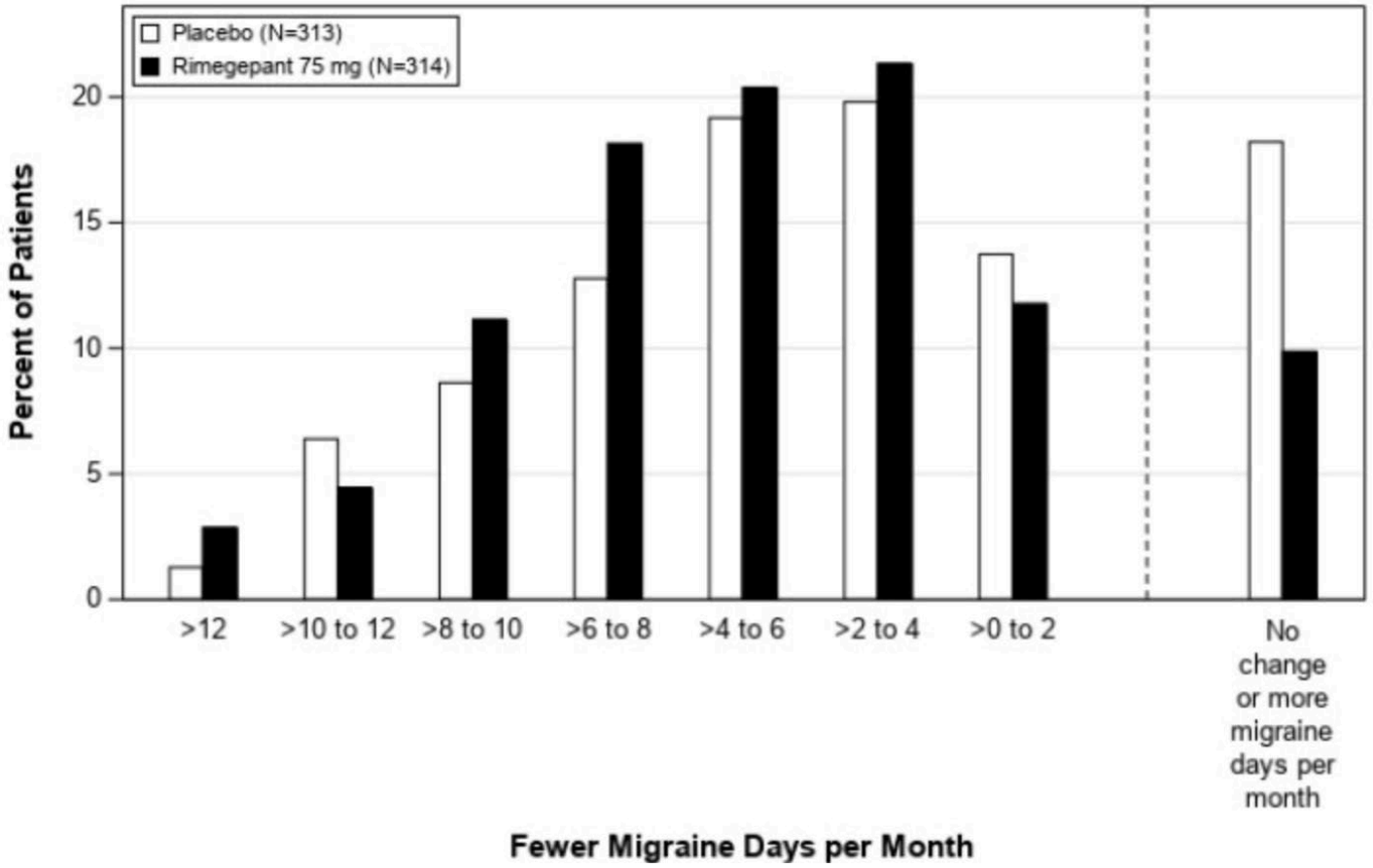
Rimegepant (Nurtec) Change Study 1

Figure 3: Change from Baseline in Monthly Migraine Days in Study 2[a]



Rimegepant (Nurtec) Change Study 2

Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Days at Month 3 by Treatment Group in Study 2[a]



Rimegepant (Nurtec) Adverse Reactions

The most common side effects of Nurtec ODT were nausea (2.7%) and stomach pain/indigestion (2.4%). These are not the only possible side effects of Nurtec ODT. Tell your HCP if you have any side effects.

Rimegepant (Nurtec) Efficacy Endpoints

Table 1: Efficacy Endpoints for the Acute Treatment of Migraine in Study 1

	Study 1	
	NURTEC ODT 75 mg	**Placebo**
Pain Free at 2 hours		
n/N*	142/669	74/682
% Responders	21.2	10.9
Difference from placebo (%)	10.3	
p-value		<0.001
MBS Free at 2 hours		
n/N*	235/669	183/682
% Responders	35.1	26.8
Difference from placebo (%)	8.3	
p-value		0.001

* n=number of responders/N=number of patients in that treatment group

Ubrogepant (Ubrelvy) Efficacy points

Table 3: Migraine Efficacy Endpoints for Study 1 and Study 2

	Study 1			Study 2	
	UBRELVY 50 mg	**UBRELVY 100 mg**	**Placebo**	**UBRELVY 50 mg**	**Placebo**
Pain Free at 2 hours					
N	422	448	456	464	456
% Responders	19.2	21.2	11.8	21.8	14.3
Difference from placebo (%)	7.4	9.4		7.5	
p value	0.002	<0.001		0.007	
Most Bothersome Symptom Free at 2 hours					
N	420	448	454	463	456
% Responders	38.6	37.7	27.8	38.9	27.4
Difference from placebo (%)	10.8	9.9		11.5	
p value	<0.001	<0.001		<0.001	
Pain Relief at 2 hours					
N	422	448	456	464	456
% Responders	60.7	61.4	49.1	62.7	48.2
p value	<0.001	<0.001		<0.001	
Sustained Pain Freedom 2-24 hours					
N	418	441	452	457	451
% Responders	12.7	15.4	8.6	14.4	8.2
p value	*NS	0.002		0.005	

Ubrogepant (Ubrelvy) Adverse Reactions

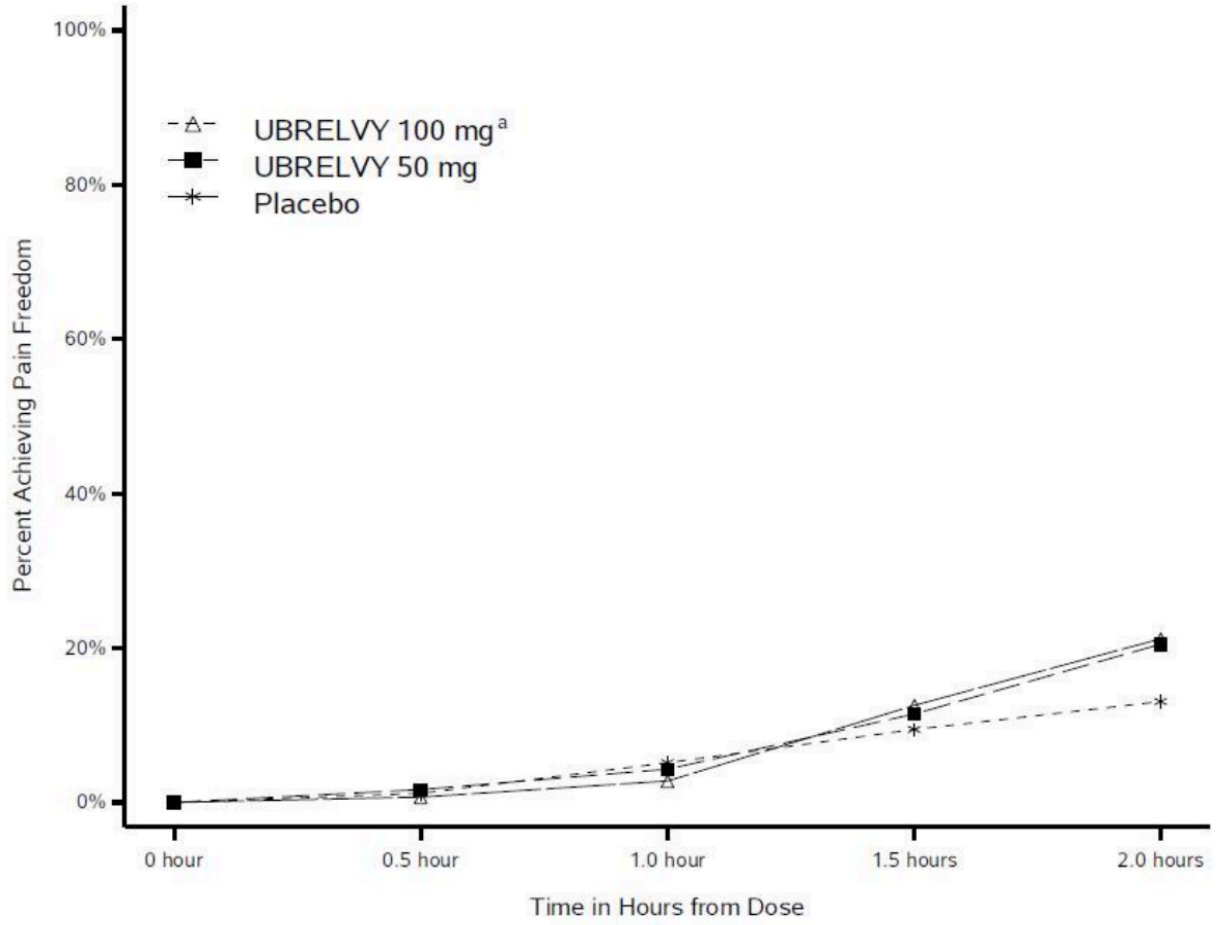
Table 2: Adverse Reactions Occurring in At Least 2% and at a Frequency Greater than Placebo in Studies 1 and 2

	Placebo (N= 984) %	UBRELVY 50 mg (N=954) %	UBRELVY 100 mg (N=485) %
Nausea	2	2	4
Somnolence*	1	2	3
Dry Mouth	1	<1	2

*Somnolence includes the adverse reaction-related terms sedation and fatigue.

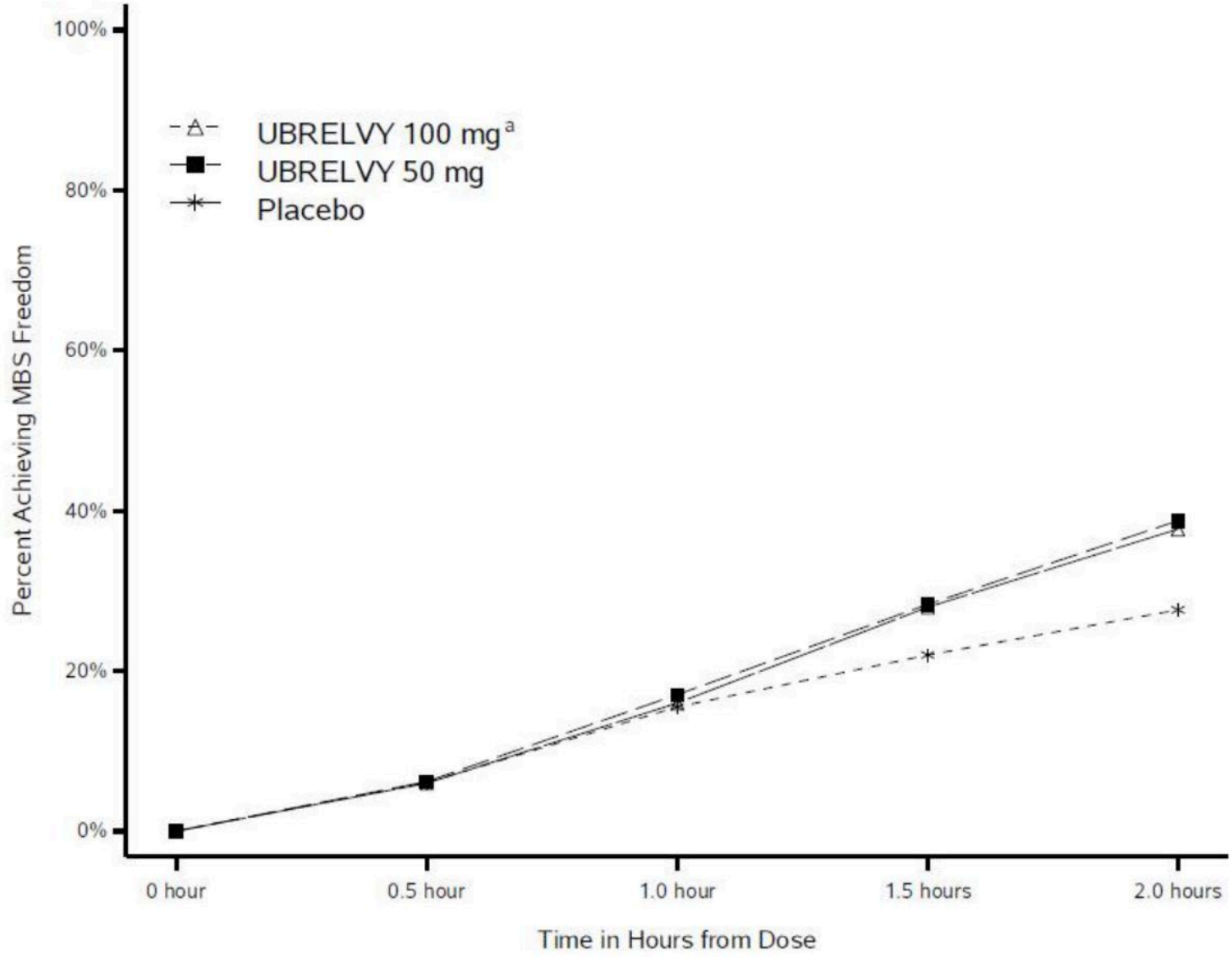
Ubrogepant (Ubrelvy) Change Study 1

Figure 1: Percentage of Patients Achieving Pain Freedom within 2 Hours in Pooled Studies 1 and 2



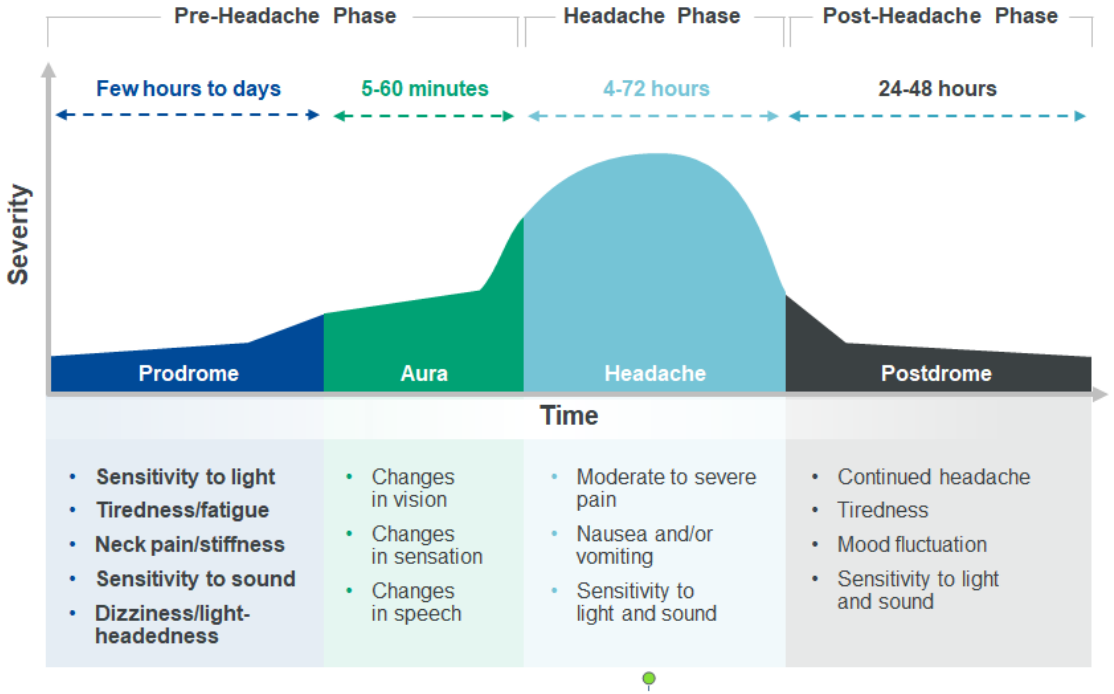
[a] The 100 mg arm was only included in Study 1.

Ubrogepant (Ubrelvy) Change Study 2



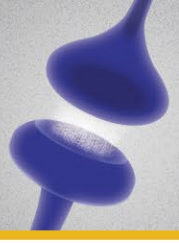
Ubrogepant in the Prodromal Phase

- Prodrome symptoms can warn patients of upcoming attack



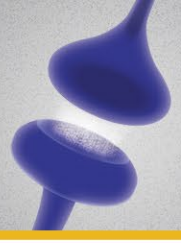
Dodick DW, et al. Lancet. 2023;402(10419):2307-2316
Dodick DW, et al. Headache. 2020;60(4):686-700
Lipton RB, et al. Poster presented at: 64th Annual Scientific Meeting of the American Headache Society, June 9-12, 2022; Denver, CO.
Dodick DW. Headache. 2018;58:4-16.

Ubrogepant in the Prodromal Phase



- Phase 3 multicenter, randomized, double-blind, placebo-controlled
  crossover study
- Objective: To determine whether treatment during the initial phase of the migraine attack, prior to the onset of headache, can attenuate the severity of the headache phase and reduce disability
- Key Inclusion Criteria
- 18-75 years of age with ≥1-year history of migraine (with or without aura)
- 2-8 migraine attacks/month with moderate to severe headache in each of the 3 months prior to screening
- Current or past use of ≥1 prescription medication for the acute treatment of migraine or preventive treatment

Ubrogepant on the Prodromal Phase



Prodrome Trial Design[1]

Visit 1 → **Screening Period (60 days)***

Randomization Criteria:

4-16 events in which prodrome symptoms led to headache pain ≥75% of the time†

OR

3 events in which prodrome symptoms led to headache pain 100% of the time[2]‡

Randomization

Double-Blind Treatment Period
(Up to 60 days, total)

1st Prodrome Event **Placebo**	→	2nd Prodrome Event **UBRELVY 100 mg**
1st Prodrome Event **UBRELVY 100 mg**	→	2nd Prodrome Event **Placebo**

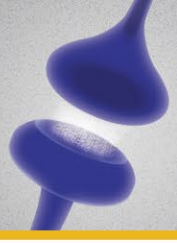
7-Day Washout§

Primary Endpoint
Absence of headache pain of moderate to severe intensity within 24 hours postdose

The 100 mg dose was the only dosage assessed. Patients were not allowed to administer a second dose.

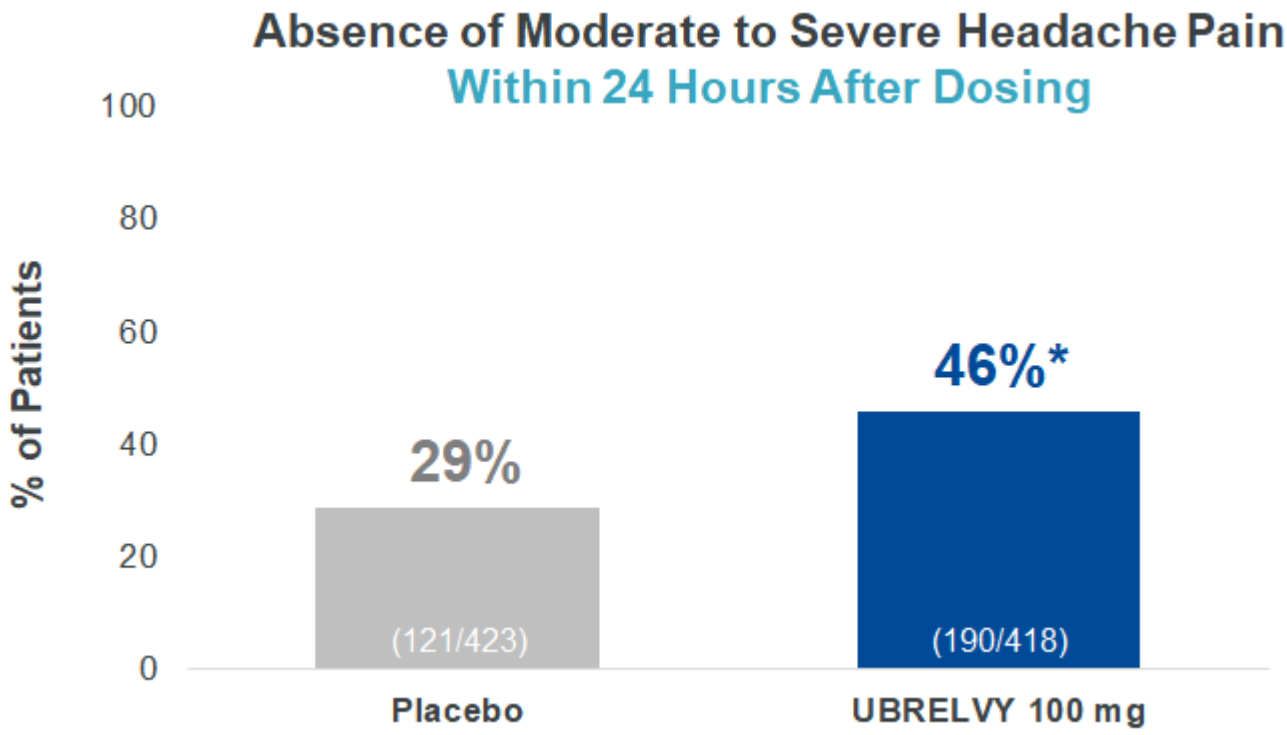
Study Design Methodology: Additional Information >

77% of patients identified their Prodromal Symptoms



- 57%: Sensitivity to light
- 50%: Tiredness/Sleepiness/Fatigue
- 42%: Neck pain/Stiff neck
- 34%: Sensitivity to sound
- 28%: Dizziness/light-headedness/vertigo/imbalance

Primary endpoint



Secondary endpoints

In addition to the primary endpoint, all three secondary endpoints met statistical significance:

Absence of moderate/severe headache within 48 hours

After 159 (41%) of 391 qualifying prodrome events that were treated with ubrogepant 100 mg and after 100 (25%) of 407 qualifying prodrome events that were treated with placebo (OR 2.13, 95% CI 1.63-2.78; *P*<0.0001)

Ability to function normally over 24 hours postdose

More participants had "no disability, able to function normally" during the 24 hours after treatment with UBRELVY 100 mg than after treatment with placebo (geometric mean of the OR 1.66, 95% CI 1.40-1.96; *P*<0.0001)

Absence of any-intensity headache within 24 hours postdose

Reported after 24% (103/434) of events treated with UBRELVY 100 mg and after 14% (61/439) of events treated with placebo (OR 1.93, 95% CI 1.39-2.66; *P*<0.0001)

Zavegepant (Zavzpret) Efficacy Endpoints

Table 2: Efficacy Endpoints in Study 1

	ZAVZPRET 10 mg	Placebo
Pain Free at 2 hours		
n/N*	147/623	96/646
% Responders	23.6	14.9
Difference from placebo (%)	8.8	
p-value	<0.001	
MBS† Free at 2 hours		
n/N*	247/623	201/646
% Responders	39.6	31.1
Difference from placebo (%)	8.7	
p-value	0.001	

* n=number of responders/N=number of patients in that treatment group

† MBS = most bothersome symptoms of photophobia, phonophobia, or nausea.

Zavegepant (Zavzpret) Adverse Reactions

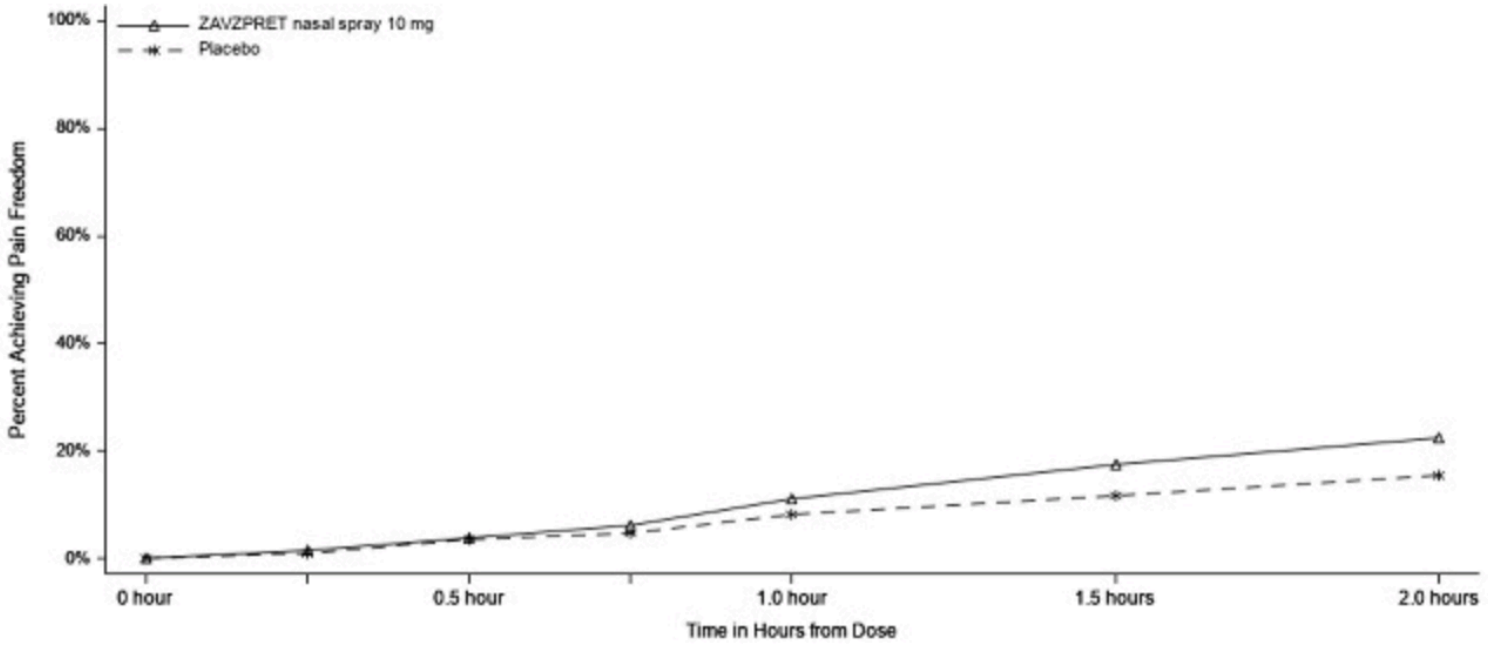
Table 1: Adverse Reactions Occurring in At Least 2% of Patients Treated with ZAVZPRET and at a Frequency Greater than Placebo in Study 1 and 2

Adverse Reaction	ZAVZPRET N=1023 %	Placebo N=1056 %
Taste Disorders*	18	4
Nausea	4	1
Nasal Discomfort	3	1
Vomiting	2	<1

* Taste disorders includes dysgeusia and ageusia

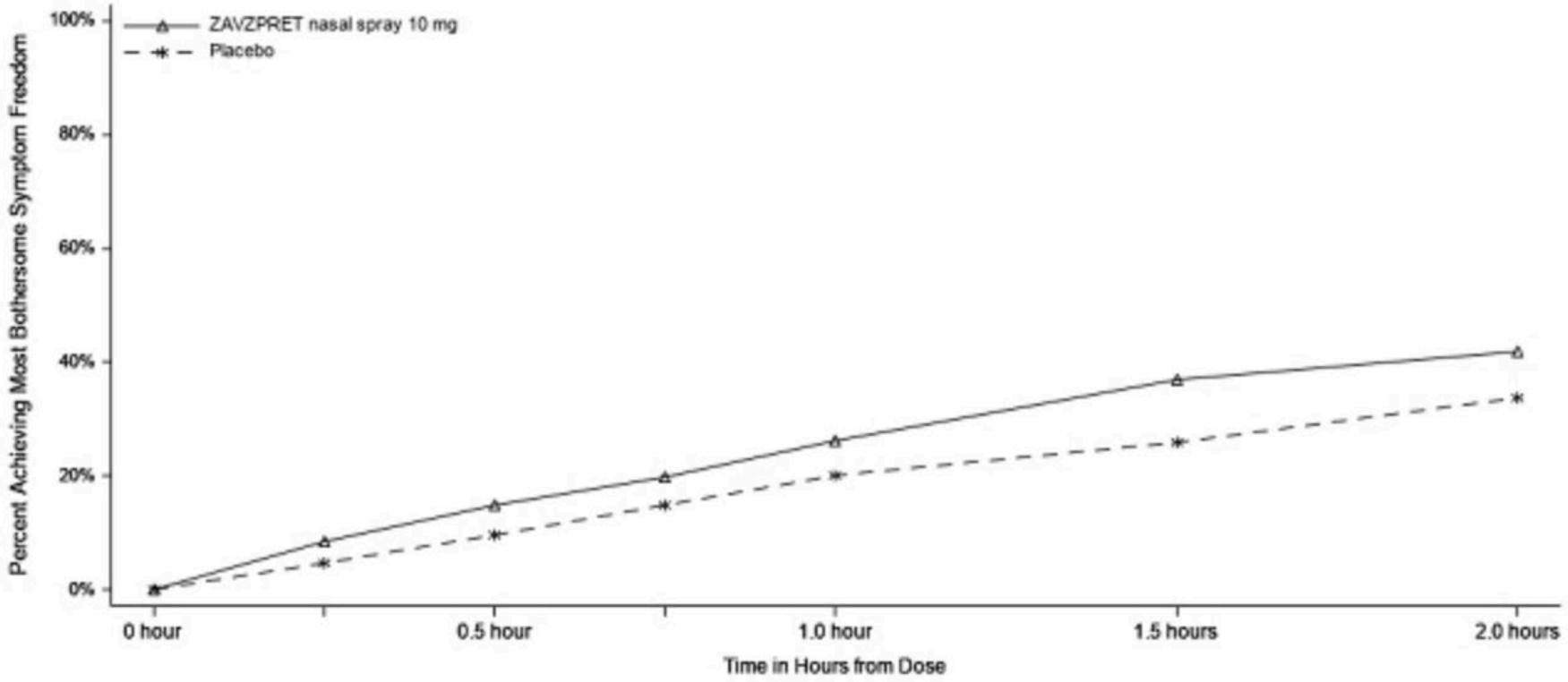
Zavegepant (Zavzpret) Change Study 1

Figure 3: Percentage of Patients Achieving Pain Freedom within 2 Hours in Study 2



Zavegepant (Zavzpret) Change Study 2

Figure 4: Percentage of Patients Achieving MBS Freedom within 2 Hours in Study 2



Lasmitidan (Reyvow)

Table 2: Migraine Efficacy Endpoints after Treatment for Studies 1 and 2

	Study 1			Study 2			
	REYVOW 100 mg	REYVOW 200 mg	Placebo	REYVOW 50 mg	REYVOW 100 mg	REYVOW 200 mg	Placebo
Pain Free at 2 hours							
N	498	503	515	544	523	521	534
% Responders	28.3	31.8	15.3	28.3	31.4	38.8	21.0
Difference from placebo (%)	13	16.5		7.3	10.4	17.8	
p-value	<0.001	<0.001		0.006	<0.001	<0.001	
MBS Free at 2 hours							
N	464	467	480	502	491	478	509
% Responders	41.2	40.7	29.6	40.8	44.0	48.7	33.2
Difference from placebo (%)	11.6	11.1		7.6	10.8	15.5	
p-value	<0.001	<0.001		0.014	<0.001	<0.001	

Pain relief at 2 hours, defined as a reduction in migraine pain from moderate or severe to mild or none, was also evaluated (see Table 3).

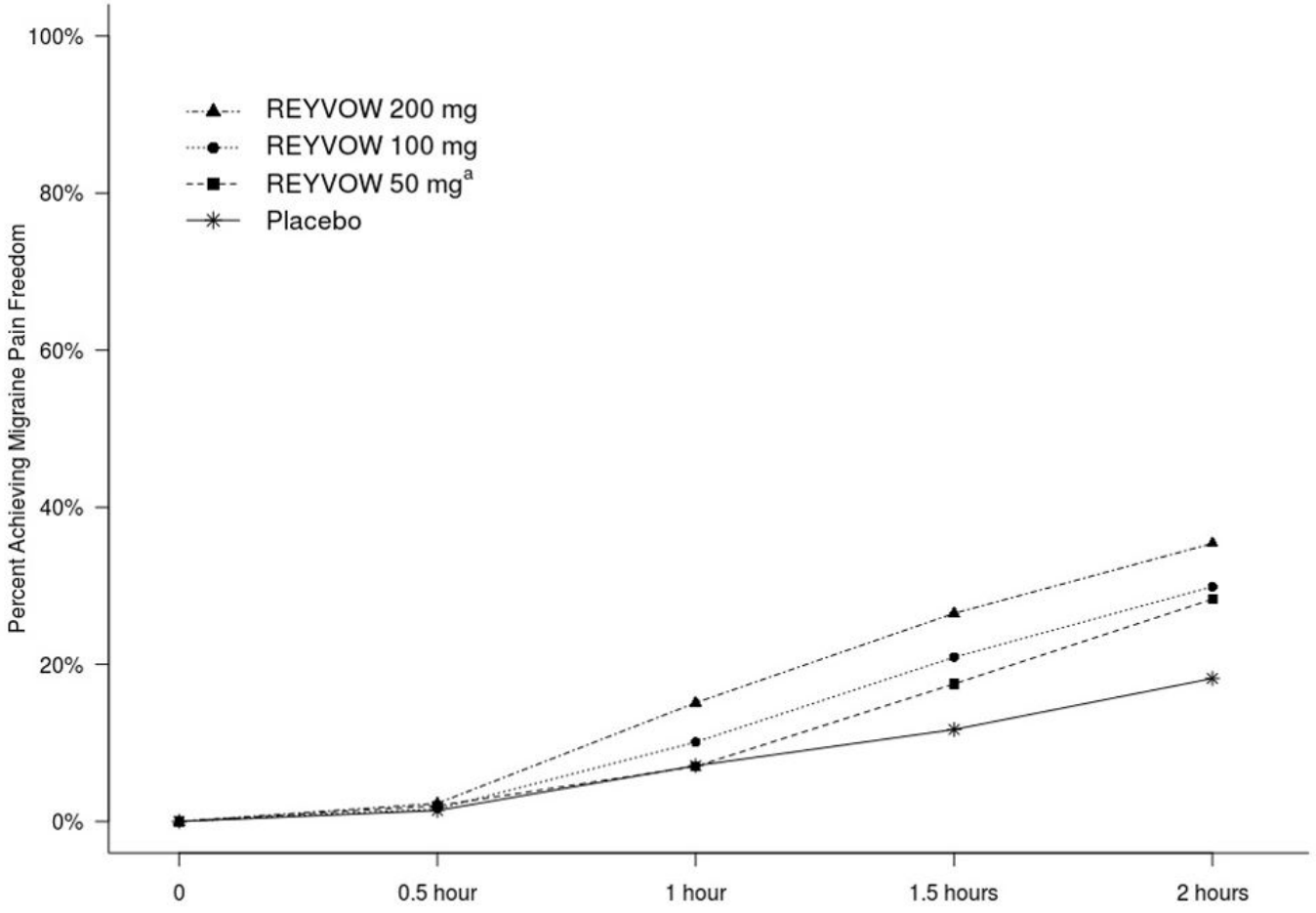
Table 3: Additional Migraine Efficacy Endpoint after Treatment for Studies 1 and 2

	Study 1			Study 2			
	REYVOW 100 mg	REYVOW 200 mg	Placebo	REYVOW 50 mg	REYVOW 100 mg	REYVOW 200 mg	Placebo
Pain Relief at 2 hours[a]							
N	498	503	515	544	523	521	534
% Responders	54.0	55.3	40.0	55.9	61.4	61.0	45.1
Difference from placebo (%)	14.0	15.3		10.8	16.3	15.9	

[a] The analysis of pain relief was descriptive and was not controlled for Type I error.

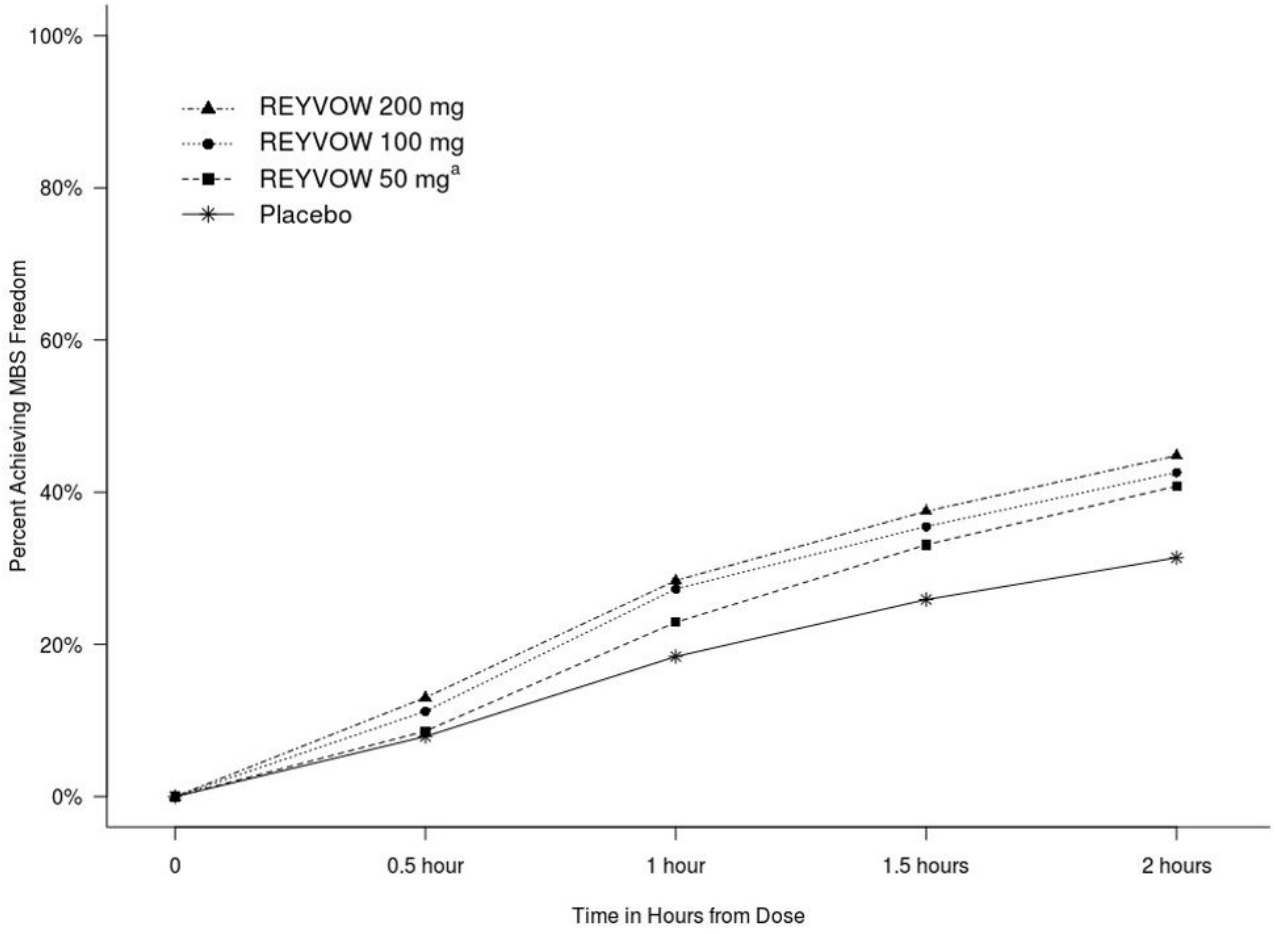
Lasmitidan (Reyvow) Pain freedom at 2 hours

Figure 1: Percentage of Patients Achieving Migraine Pain Freedom within 2 Hours in Pooled Studies 1 and 2



Lasmitidan (Reyvow) MBS

Figure 2: Percentage of Patients Achieving MBS Freedom within 2 Hours in Pooled Studies 1 and 2



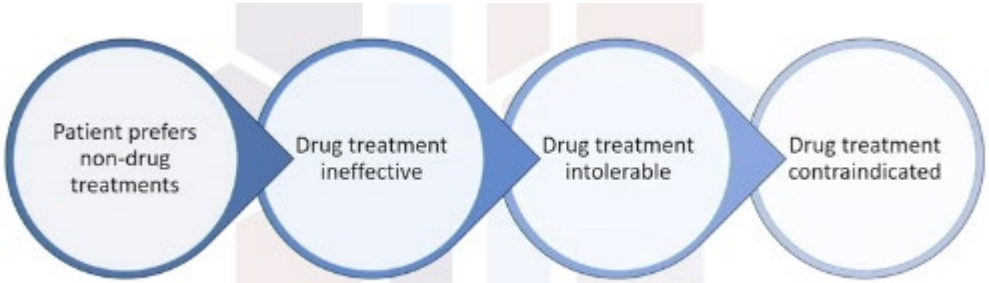
Lasmitidan (Reyvow) Adverse Reactions

Table 1: Adverse Reactions Occurring in ≥2% and at a Frequency Greater than Placebo in Studies 1 and 2

Adverse Reaction	REYVOW 50 mg N=654 %	REYVOW 100 mg N=1265 %	REYVOW 200 mg N=1258 %	Placebo N=1262 %
Dizziness	9	15	17	3
Fatigue[a]	4	5	6	1
Paresthesia[b]	3	7	9	2
Sedation[c]	6	6	7	2
Nausea and/or Vomiting	3	4	4	2
Muscle Weakness	1	1	2	0

[a] Fatigue includes the adverse reaction related terms asthenia and malaise.
[b] Paresthesia includes the adverse reaction related terms paresthesia oral, hypoesthesia, and hypoesthesia oral.
[c] Sedation includes the adverse reaction related term somnolence.

AHS recommends non-drug Acute Treatment of Migraine When

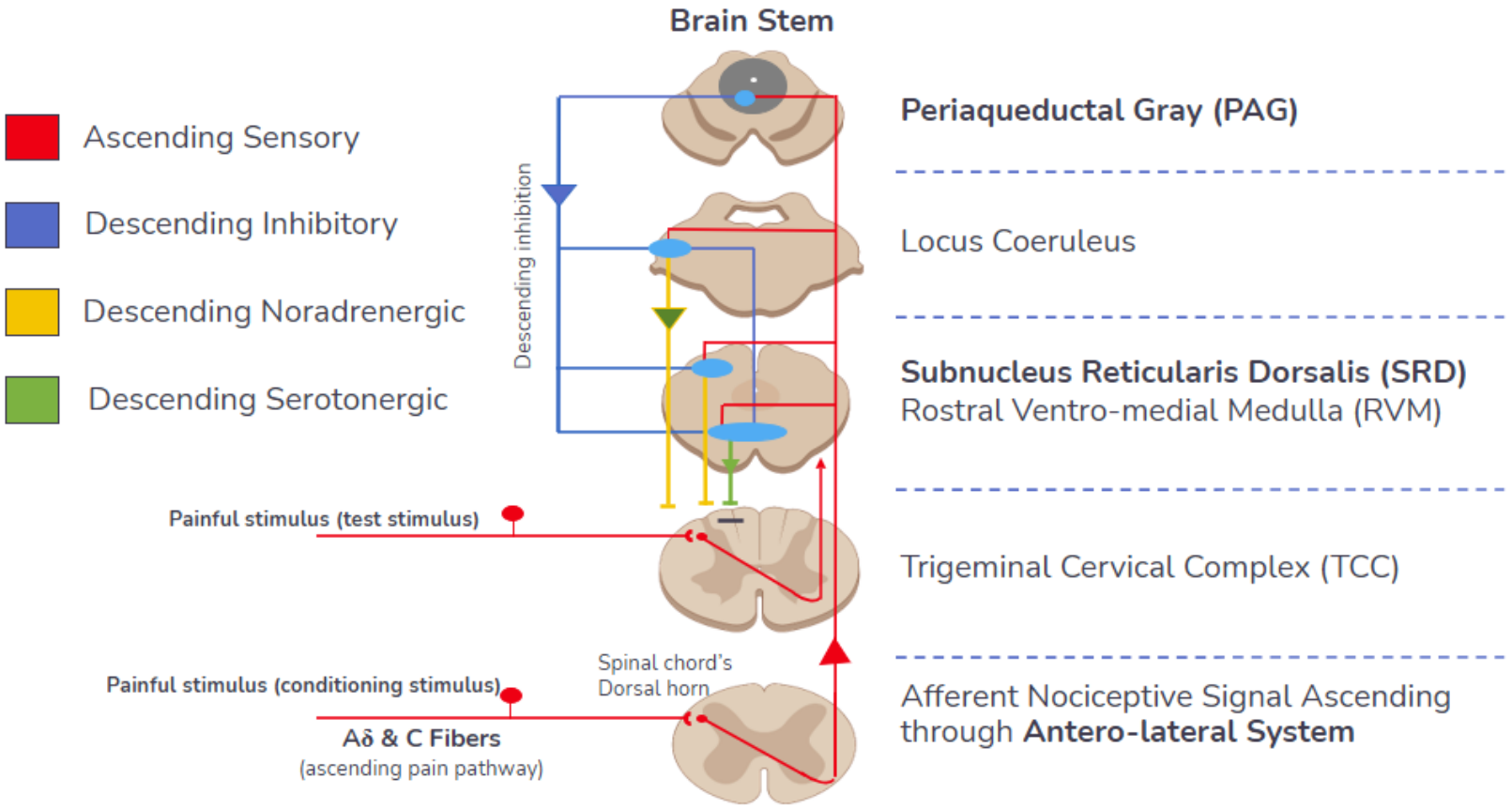


FDA Approved Neuromodulation in Migraine

Device Comparison

Device	Nerivio® 	Cefaly® 	gammaCore® 	Relivion® 	SAVI Dual™ 
Company	Theranica	Cefaly	electroCore	Neurolief	eNeura
Mechanism	REN –Remote Electrical Neuromodulation	TENS – gate theory of pain	nVNS – Vagus nerve Stimulation	eCOT-NS - External Combined Occipital and Trigeminal Nerve Stimulation (TENS)	sTMS – Single-pulse transcranial magnetic stimulation
Indication	Acute & Preventative, 12+	Acute & Preventive, 18+	Acute & Preventive, 12+	Acute, 18+	Acute & Preventive, 12+
RX/OTC	Rx	OTC	Rx	Rx	Rx
Usage	45 min, on upper arm	1 hour, on head	4 min, on neck	1 hour, on head	15-30 min, on head
Digital	App, Electronic Diary, Personalized Feedback, GIER	-	-	App	Electronic Diary
Pivotal trails ITT	252	106	248	131	164
Pain free, 2 h	37.4% (placebo:18.4%),p<0.005	17% (placebo: 7%), NS	30.4% (placebo: 19.7%), NS	46% (placebo: 12%), p<0.001	39% (placebo: 22%), p=0.0179
Pain relief, 2 h	67% (placebo: 38%), p<0.0001	N/A	41% (placebo: 28%), p<0.05	60% (placebo: 37%), p=0.018	72% (placebo: 67), p=0.4988
Pain relief, 24 h	39%, at 48 Hours	6%, at 24 h	N/A	36%, at 24 h	29%, at 24 h
Reduction in MMDs	4.0 (placebo: 1.3), p=0.00002	2.0 (placebo: 0.3), NS	2.3 (placebo: 1.5), p=0.04 (mITT only; NS in ITT)	N/A	

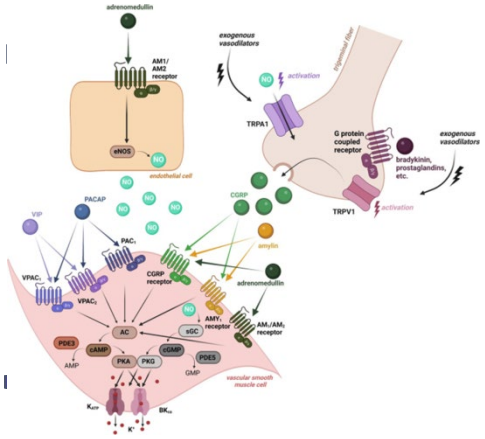
Brainstem MOA



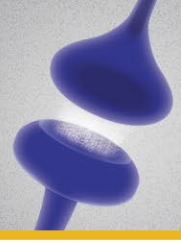
Ramaswamy 2021, Bouhassira, 1992; Ossipov, 2010; Yarnitsky, 2010

Emerging Targets for Migraine

- Pituitary adenylate cyclase activating peptide (PACAP38 and 27)
- Cannabinoids
- Insulin-like growth factor (IGF-1) nasal spray
- Liraglutide glucagon-like peptide-1agonist for IIH
- Selective nitric oxide synthase inhibitors
- Histamine receptor modulators
- 5-HT2B/2C receptor antagonist xc101-D13H for prevention
- Others



Abortive Treatment of Cluster Headache



- Neuromodulation devices
- Oxygen Therapy
- SC Sumatriptan
- IN Zolmitriptan
- Galcanezumab*
- Psychedelic Research
- SPG block: Intranasal viscous lidocaine 2%
- Combination Therapies
  - Oxygen therapy plus SC Sumatriptan
  - SC Sumatriptan plus devices (Gammacore)

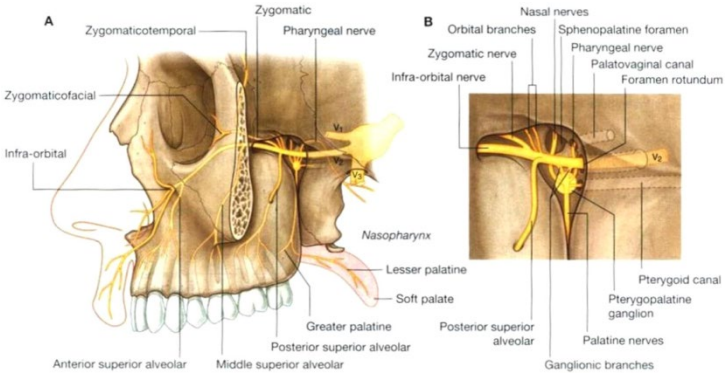
Neuromodulation Devices

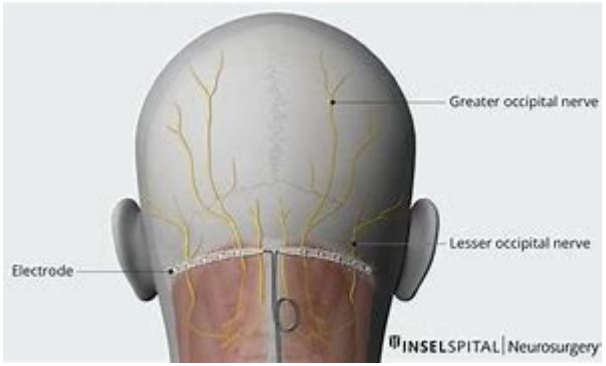
- Non-invasive Vagus Nerve Stimulation (nVNS) Gammacore
  - Delivers mild electrical impulses to the VN when applied to the skin of the neck
  - The BN plays a key role in the autonomic nervous system, its stimulation can modulate pain pathways
  - Effective in about 35 – 40% of patients for episodic cluster headaches with good tolerability
  - FDA approved in 4/2017, prescribed for home use

"Cluster Headache." The Migraine Trust. The Migraine Trust, n.d. Web. 30 Nov. 2016. https://www.migrainetrust.org/about-migraine/types-of-migraine/other-headache-disorders/cluster-headache/.

Sphenopalatine Ganglion Stimulation

- More invasive, requires implantation of a small stimulator to target the SPG, involved in headache pain transmission
- Occipital Nerve Neuromodulation
  - Explored in chronic cluster with mixed results



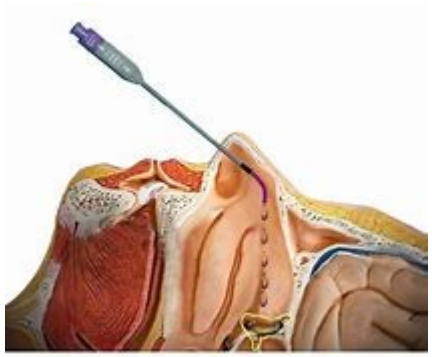


Tepper, S. Volume57, IssueS1:Neurostimulation
April 2017, Pages 14-28

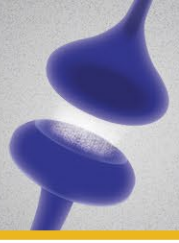
Kollenburg L.The Journal of Headache and Pain.
Volume 25:139 (2024)

Sphenopalatin Ganglion Block

- Evolving treatment approach for cluster headache
- Targets the SPG, associated with the trigeminal-autonomic reflexes involved in cluster headaches
- Sphenocath and other devices
  - Specialized applicators that allow for easier, more precise trans-nasal delivery of anesthetics to the SPG

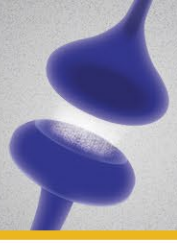


Oxygen Therapy



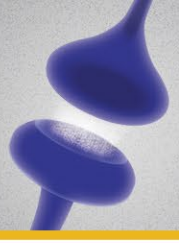
- Advances
  - Demand-Valve Oxygen systems: controls the flow of O2, more targeted
  - Portable Oxygen Systems
    - Increasing accessibility

Triptans for Cluster Headaches



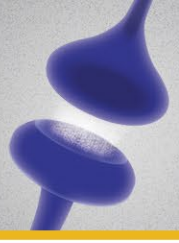
- SC Sumatriptan, gold standard, 75% relief in 15 minutes
  - Advances: needle free jet injections
- Intranasal Zolmitriptan
  - Good option for needle phobic patients

CGRP Antagonists



- Galcanezumab
  - Primarily preventive, frist mAb approved for episodic cluster prevention
  - Emerging data suggests that it may have an abortive effect, particularly when adminstered during high frequency episodic attacks

Intranasal Lidocaine

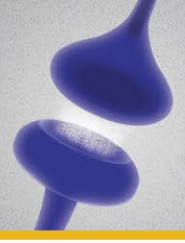


- Targets the SPG, implicated in cluster headaches
- Can provide relief in 30 to 40 % of patients within 10 to 15 minutes
- We use Dr. Morris Maizel's protocol

Combination Therapies

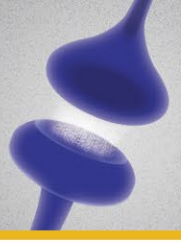
- Oxygen + Triptans
- Neuromodulation plus Triptans
- Others

Research



- Psychedelic
  - Psilocybin and LSD
  - Act on serotonin receptors in the brain, similar to triptans but seem to have longer lasting effect in breaking cluster cycles
  - MOA: disrupt abnormal brain activity in the hypothalamus, involved in circadian rhythm
- Ketanserin (serotonin recepton agonist)
- Remote neuromodulation

Thank you for your attention



- Questions?