Long Road to Effective Migraine Therapies

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Setpember 24, 2022

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Migraines

For two centuries migraines were thought to be a vascular disorder involving constriction of blood vessels followed by dilation=PAIN

We know now that migraines start in the brain with abnormal activation of multiple networks, and the Trigeminovascular complex is key

This has been accomplished thru better understanding of molecular biology, receptor pharmacology , neurotransmitters and neuropeptides in the TVC

This has resulted in an explosion of new, more effective drugs that target the neuropeptides or receptors i.e. erenumab galcanezamab fremanezumab eptinezumab rimegepant ubrogepant atogepant,

FYI

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- Migraines affect over 36 million in US
- Prevalence in one year worldwide is 15%
- They account for 52% of visits to PCP, 40% need prophylaxis and 13% will obtain it
- In 2025 there will be a shortage of Neurologists by 18%
- New movement to educate PCPs to better diagnose and treat migraine patients

- Migraines can be traced back to Mesopotamian ritual texts 4000 years ago. Headaches were thought to be spiritual rather a physical ailment
- Egyptians had the first descriptions of migraines in the Ebers Papyrus(1550BC)
- Hippocrates was the first to categorize headaches into different types and were attributed to physical and pathological states
- Surgical treatment of headache has evolved throughout history ie trepanation, craniotomy

Ebers Papyrus,1550BC

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- Found in Egypt in 1870s and is one of the oldest medical texts
- It contains the first documented description of migraine and proposes surgical treatment

- Prehistoric era was marked by lack of understanding of the human body and disease
- Trepanation, removing a piece of skull, dates back to Neanderthals 9000 years ago. Thus, giving evil spirits an escape route
- Tiu was the evil spirit of headache in the Mesopotamia era and treatment was based on appeasement thru trepanation or medicinal formulas

Trepanated skull

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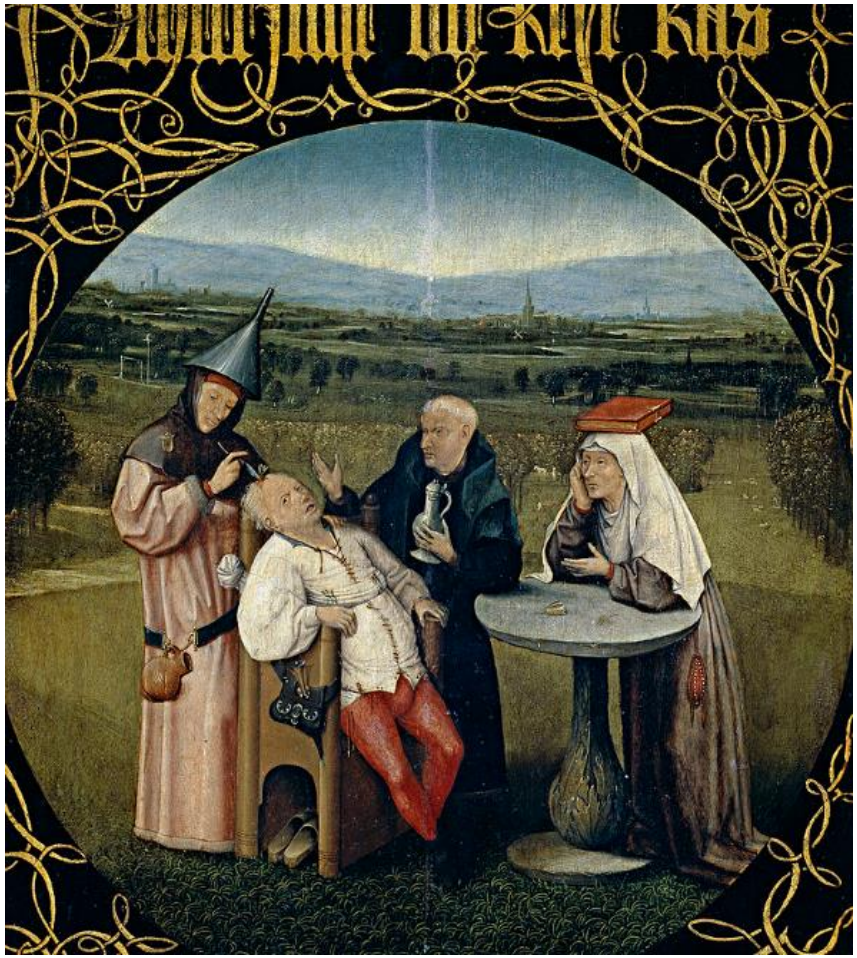
Around 700BC Greek mythology said Hephaestus performed a craniotomy on Zeus to relieve his excruciating headache caused by a mass growing inside his head using a double-headed ax

But alas, it was his daughter Athena

- Painting completed around 1494,by Hieronymus Bosch showing medieval trepanation



- Middle Ages saw an increase in medical treatment for headache rather than trepanation, usually reserved for severe cases
- Renaissance period saw more trepanation due to use of firearms, but still reserved for refractory cases
- 18th-20th centuries showed an increase in scientific methods, bedside exam and less dependence on the spiritual doctrines of the 18th century. So, bloodletting and fluid drainage were main methods!

- Prince Rupert of the Rhine, an English commander had a trepanation in 1667 and lived until 1682!
- He had complete relief of his severe headache

- Humoral medicine recommended balancing body fluids to restore the right balance/ eukrasis. Four humours are blood, phlegm, yellow and black bile. If drug treatments for headache failed, then humoral substances could be withdrawn.

  -Bloodletting was a common treatment for headache either from a peripheral vein or one in the forehead, or artery

  -Cupping and blistering –placing a heated glass on the skin to blister, to balance humours

- Cauterization was used if above treatments were not helpful. A hot iron was applied to the head
- Abulcasis (936-1013) was surgeon to the king of Spain, would apply a red hot iron and if not successful took garlic and placed it in an incision in each temple
- Blistering plasters and cauterization were still used by Claude Pouteau(1725-75) a French surgeon at Hotel Dieu of Lyon

Ouch

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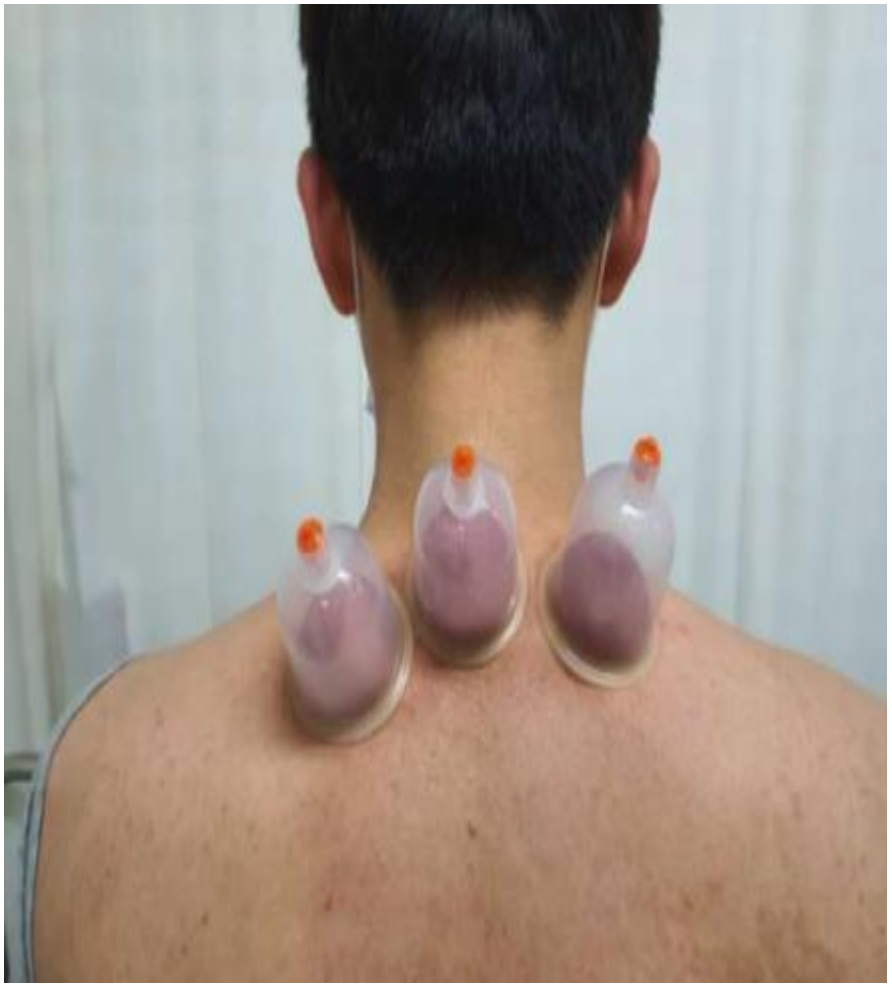

Various other methods

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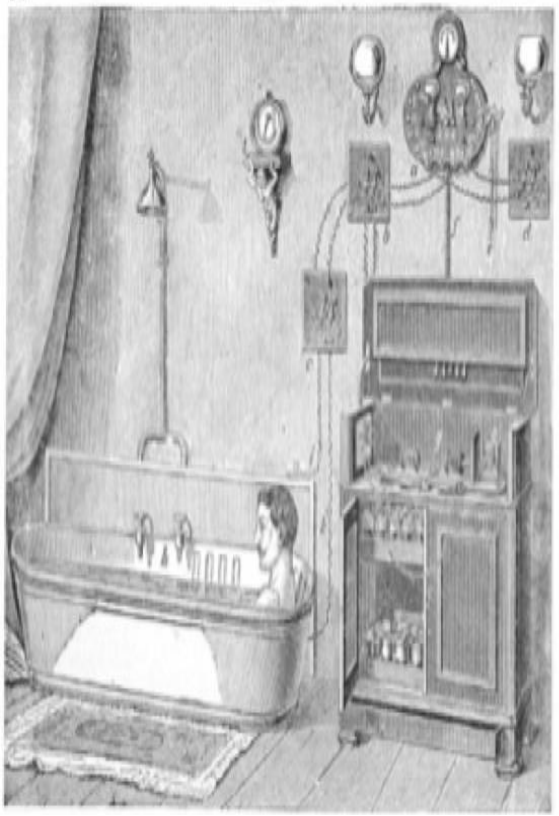
Soft oil into the ear was used

Middle of the 18th century electricity was used as a treatment including use of fish, eels of South America

A hydroelectric bath was used as treatment by many but at the turn of the century Paul Mobius,(1845-1907) a German physician doubted its effect except for a placebo or suggestible component

William Gowers(1845-1915) was doubtful of repeated galvanization of the sympathetic nerves as treatment of migraines, " rarely permanent relief"

A



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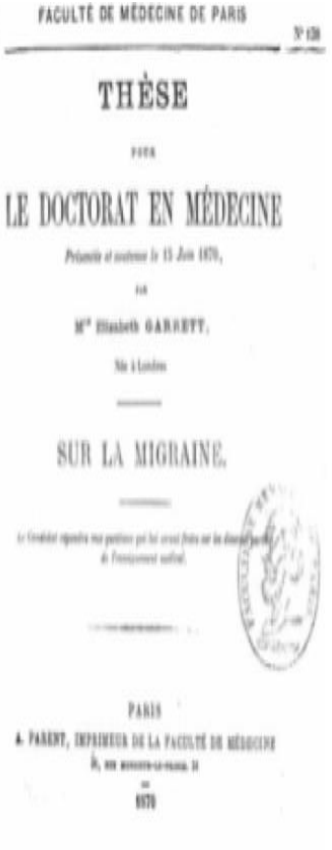


FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MÉDECINE

Présentée et soutenue le 15 Juin 1870,

PAR

Mlle Elisabeth GARRETT,

Née à London

SUR LA MIGRAINE.

PARIS

A. PARENT, IMPRIMEUR DE LA FACULTÉ DE MÉDECINE

1870

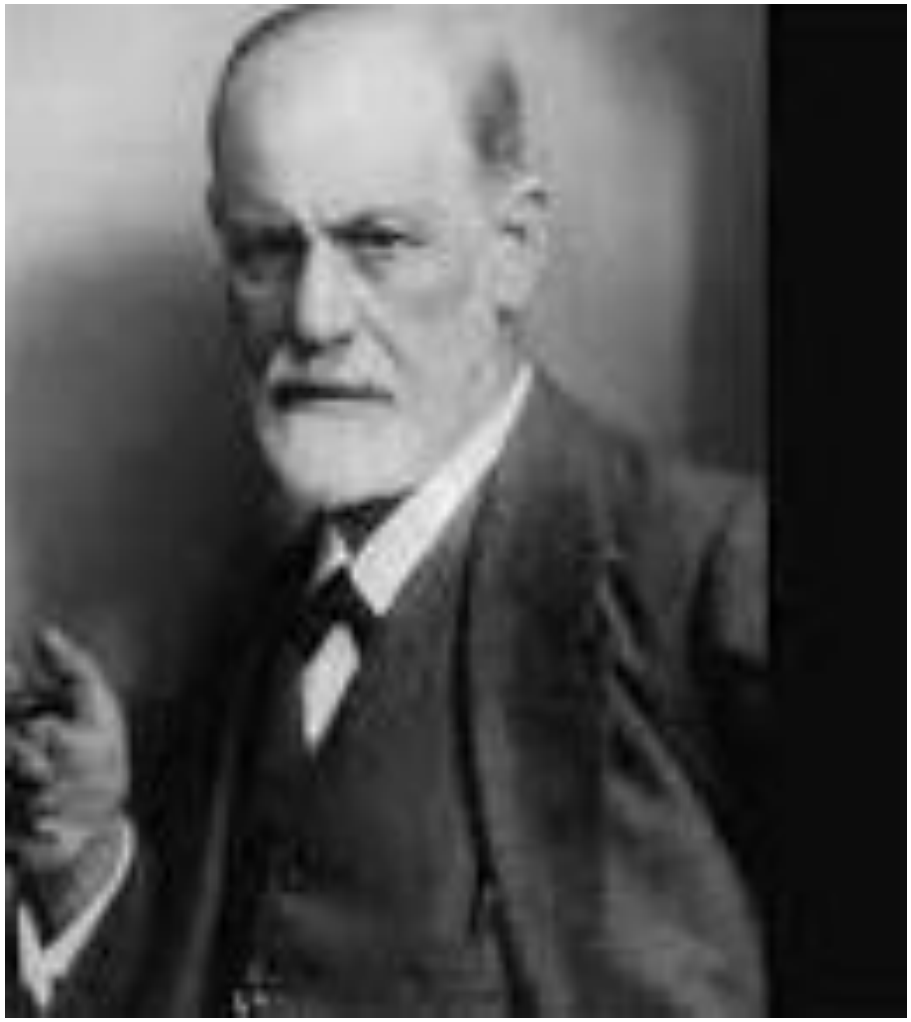
- By 1800 headaches were classified into categories, primary, secondary and cause i.e. external, internal, idiopathic, febrile, inflammatory hysterical etc.
- Beginning of 20th century migraine headache was an established entity, but cause and treatment was still difficult to establish
- Dr Harvey Cushing(1869-1939) performed decompressive craniotomies with poor success as he favored the idea of ICP as etiology

- Early 1900's migraines were still thought to be vasospastic so various surgical procedures were employed to cause vasodilation
- Cervical sympathetic surgeries, periarterial sympathectomy of the temporal artery
- Walter Dandy, American neurosurgeon(1886-1946) operated on cervical and 1st thoracic ganglion- reporting success in 2 patients for 7 and 4 months with migraines

- 1950-60s migraines were described as vascular headaches and divided into classical and common migraines
- Bickerstaff described basilar artery migraine
- Aura was thought to be from vasoconstriction and the pain vasodilation; Researchers in the 50s realized vasodilation per se would not cause headache and that likely there were additional nociceptive phenomena around the blood vessels
- Polypetides labeled "Neurokinins" were thought to be released causing a sterile inflammatory reaction

- Psychological disorders were thought to be a major factor
- "headache is a psychosomatic expression . . . of tension or anxiety"
- "Scotomatas of migraine are related to previous visual psychological trauma, which are repressed"
- "Unexpressed emotions will never die. They are buried and will come forth later in uglier ways"

-- Sigmund Freud



- Synergan, was the first ergot discovered in 1921,and used extensively. Isolated by Arthur Stoll
- Even combination ergots were used thru the ‘90s

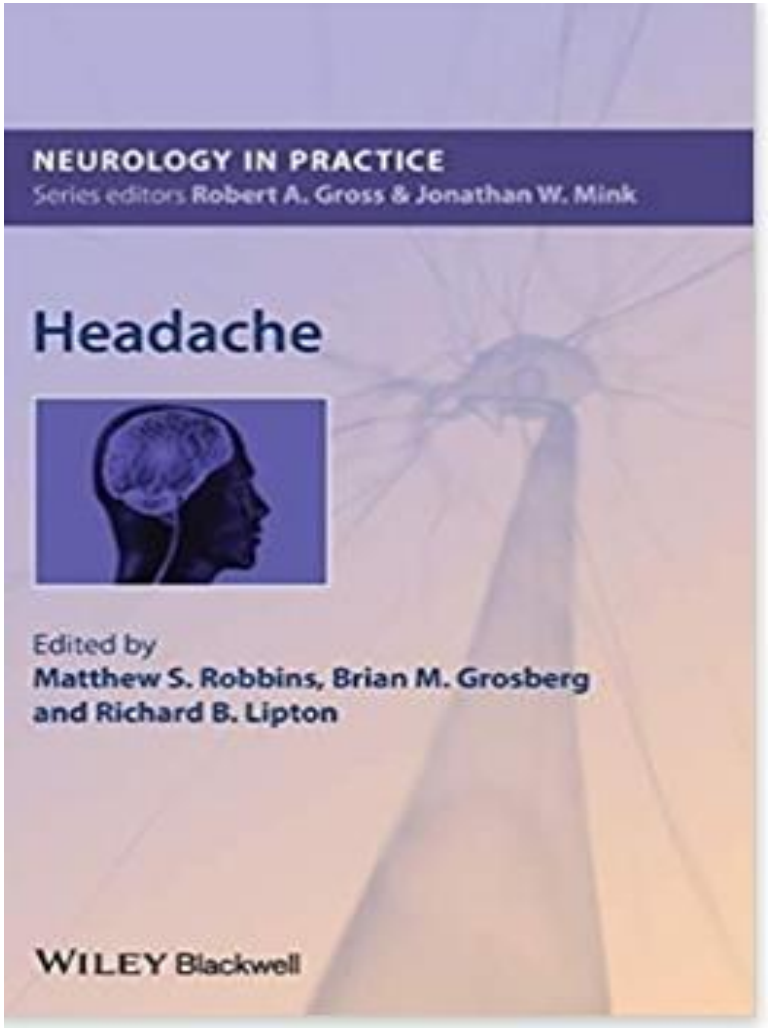
Past therapies were borrowed to treat migraine patients. Only a few were FDA approved.

Inderal, Topamax, Elavil and Depakote were used for other primary indications and secondarily for migraine treatment.

- Federigo Sicuteri et al found with migraines an increase in 5-hydroxyindolacetic acid, a serotonin metabolite
- The success of methysergide/Sansert supported this finding and the prophylactic of choice in 50s. Its use declined in 60s with the findings or retroperitoneal and intrathoracic fibrosis. Its an ergot derivative that is a congener of lysergic acid diethylamide/LSD
- Some drugs were noted to increase migraines including MAO inhibitors and birth control pills

- AEDs started to be used in the 60's due to eeg findings in migraine patients
- Cyproheptadine was introduced for prophylaxis
- Combo ergot/ belladonna alkaloids and phenobarbital drugs were used
- TCAs were more effective that placebo for prophylaxis i.e. amitriptyline, imipramine
- Propranolol approved in 1976 by FDA, after several studies, for prophylaxis of migraine without aura

- AMA formed the AHS in June 1959 which legitimized migraines and led to an increase in research due to better classification criteria
- The journal Headache started in 1961
- First headache clinic established in NY 1945 by Drs Arnold Freidman, Houston Merritt and Charles Brenner
- Headache treatment centers proliferated in the ‘70s leading to an increase in practitioner expertise and pharmacologic therapies



- First edition of Headache April 1961

1980's

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- Cephalgia, 1988 published first version of ICHD
- Jes Olesen in early 80s observed that blood flow changes did not respect large arterial territories, but spread at a slow rate c/w the cortical phenomena of " spreading depression of Leao"
- Moskowitz showed plasma extravasation from blood vessels with stimulation of the TN in animals and suspected the trigeminal vascular system played a greater role than a simple vascular disorder

- Throbbing pain is secondary to the activation of the trigeminovascular pathway. Peripheral sensitization is responsible for the throbbing pain, worse with movement etc.
- Nociceptive neurons that innervate the dura are stimulated and release vasoactive neuropeptides i.e. CGRP
- TVP conveys nociceptive info from meninges to central areas of the brain and then to cortex

- The hypothalamus is implicated as a potential origin of the migraine attack
- Migraines are typically triggered by a change in homeostasis (did not sleep, change in sleep pattern, off with meals skipping a meal)
- Functional imaging is supportive of the hypothalamus involvement in the premonitory phase

- 1984 a Glaxo scientist synthesized GR43175 a 5HT1b, d serotonin agonist—sumatriptan. Not FDA approved as a sq injection until 1992 and the tablet in 1995
- Biofeedback was popular; calcium channel blockers and valproate were tested and used in clinical practice
- Valproic acid was being used 1987-88. Some data supported cortical excitability. Also an observation by Nishikawa that valproic acid, a GABA mimetic agent, acts on GABA receptors in dorsal raphe resulting in decreased firing of serotonergic cells
- Raskin, Ninan Matthews, started using valproate in 1988

- Valproic acid was not FDA approved until 1995
- 1990's were the decade of the triptans.
- Initially with sumatriptan injection in 1992 followed by the oral triptans, nasal sprays
- In 2000s more promise with CGRP blockers
- Also further trials with gabapentin and topiramate

CGRP

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-Research in the 90s with CGRP found it was closely related to migraine attacks

-Antagonism of CGRP pathway aborts migraine pain, offering new therapies

-A 37 amino acid neuropeptide encoded by calcitonin gene (CALCA) in the family of amylin, calcitonin and adrenomedullin. A potent vasodilator found in CNS,PNS, cardiovascular and GI systems

-2 isoforms: alpha in sensory neurons and beta in the enteric neurons

CGRP

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- Evidence supports CGRP as playing a key role in migraine pathogenesis:
  - It is present in afferents innervating meningeal blood vessels
  - Enhances synaptic transmission mediated by glutamatergic signaling
  - There is an elevation of CGRP level in jugular vein blood during attacks
  - IVCGRP will induce a migraine attack in migraine patients, but not in healthy volunteers

CGRP

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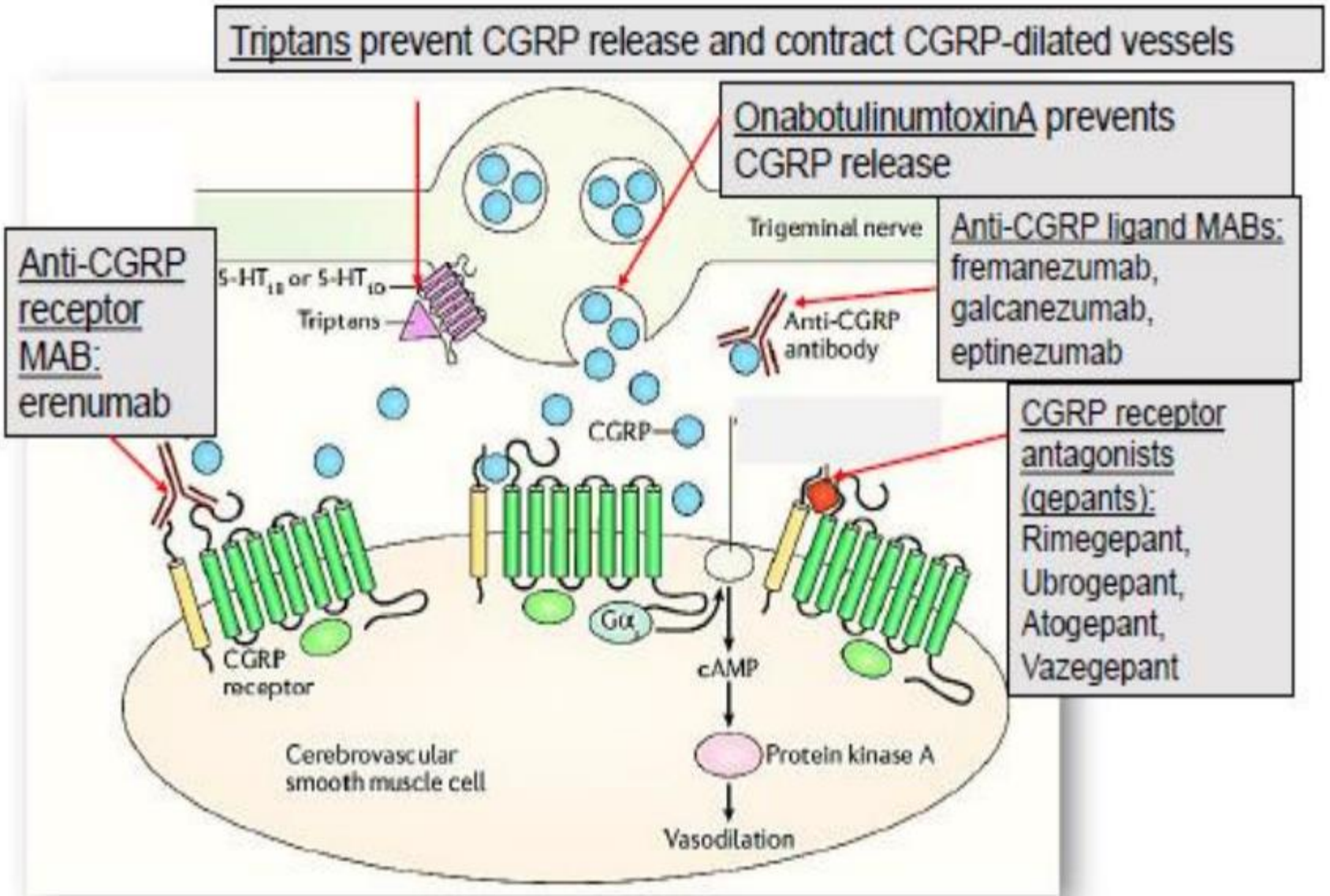
- This led to the development of drugs that modulate CGRP, to prevent episodic and chronic migraines
- Small molecule CGRP-RA show clinical efficacy acutely and prophylactically in trials, supporting the role of CGRP in migraine
- Large molecule mAbs that bind CGRP or block receptors show consistent efficacy in studies


Triptans prevent CGRP release and contract CGRP-dilated vessels
OnabotulinumtoxinA prevents CGRP release
Anti-CGRP receptor MAB: erenumab
Anti-CGRP ligand MABs: fremanezumab, galcanezumab, eptinezumab
CGRP receptor antagonists (qepants): Rimegepant, Ubrogepant, Atogepant, Vazegepant
Trigeminal nerve
5-HT1B or 5-HT1D
Triptans
Anti-CGRP antibody
CGRP
CGRP receptor
Gα
cAMP
Protein kinase A
Cerebrovascular smooth muscle cell
Vasodilation

Ditans

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- Lasmiditan- first of the ditans approved in fall 2019
- Targets 5HT1F receptor to inhibit trigeminal nerve firing. Approved for acute treatment
- Crosses the BBB therefore dizziness(15% with 100mg), sedation can occur. Recommendation to not drive for 8 hours after dosing
- No vasoconstriction like the triptans
- No contraindication for those with vascular disease or risk of heart attack or stroke
- Pain freedom at 2hrs is 33-39% in SAMARAI,SPARTAN studies

Lasmiditan/Reyvow

Pain relief at 2 hours

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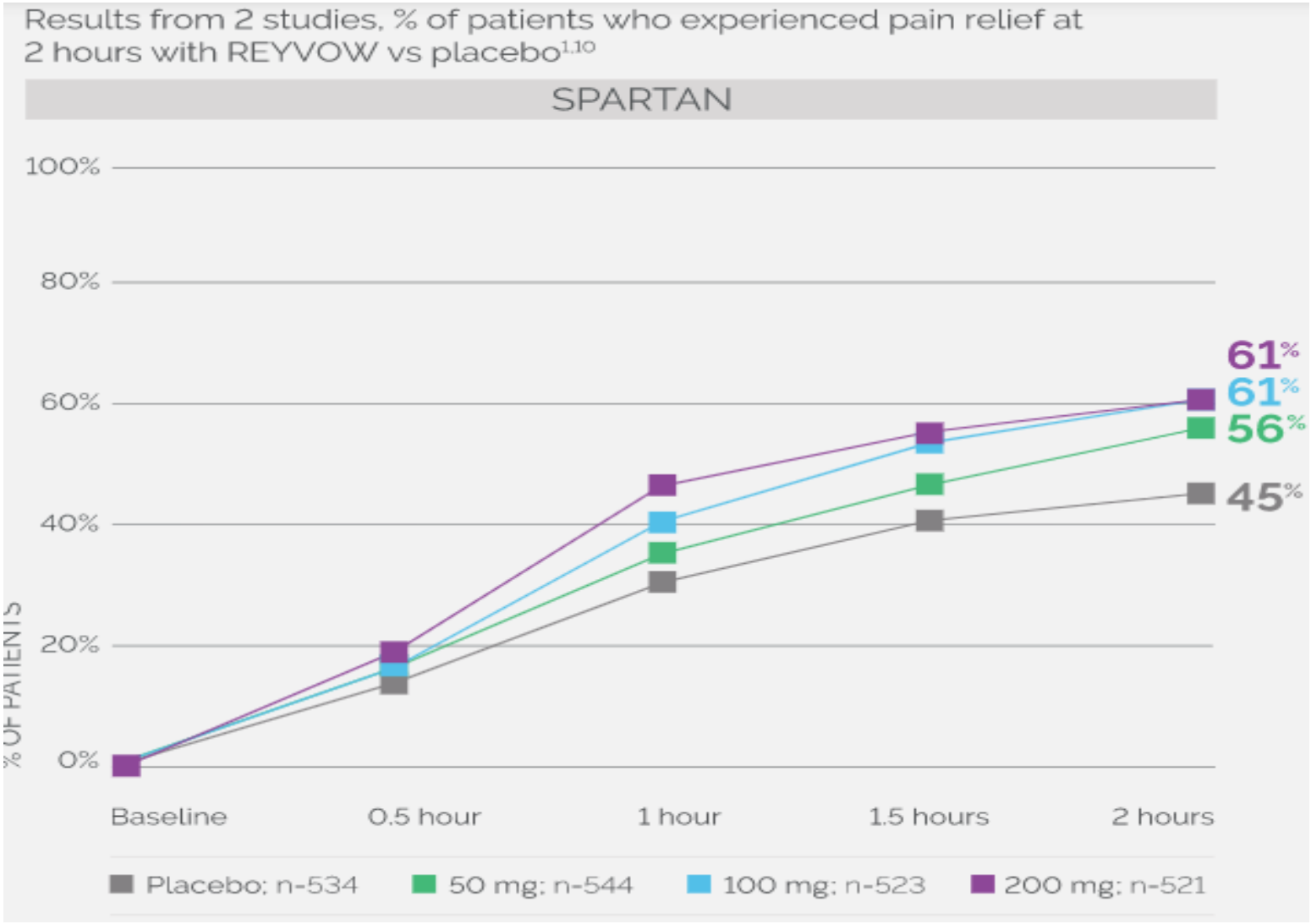

Lasmiditan

Pain freedom at 2 hours

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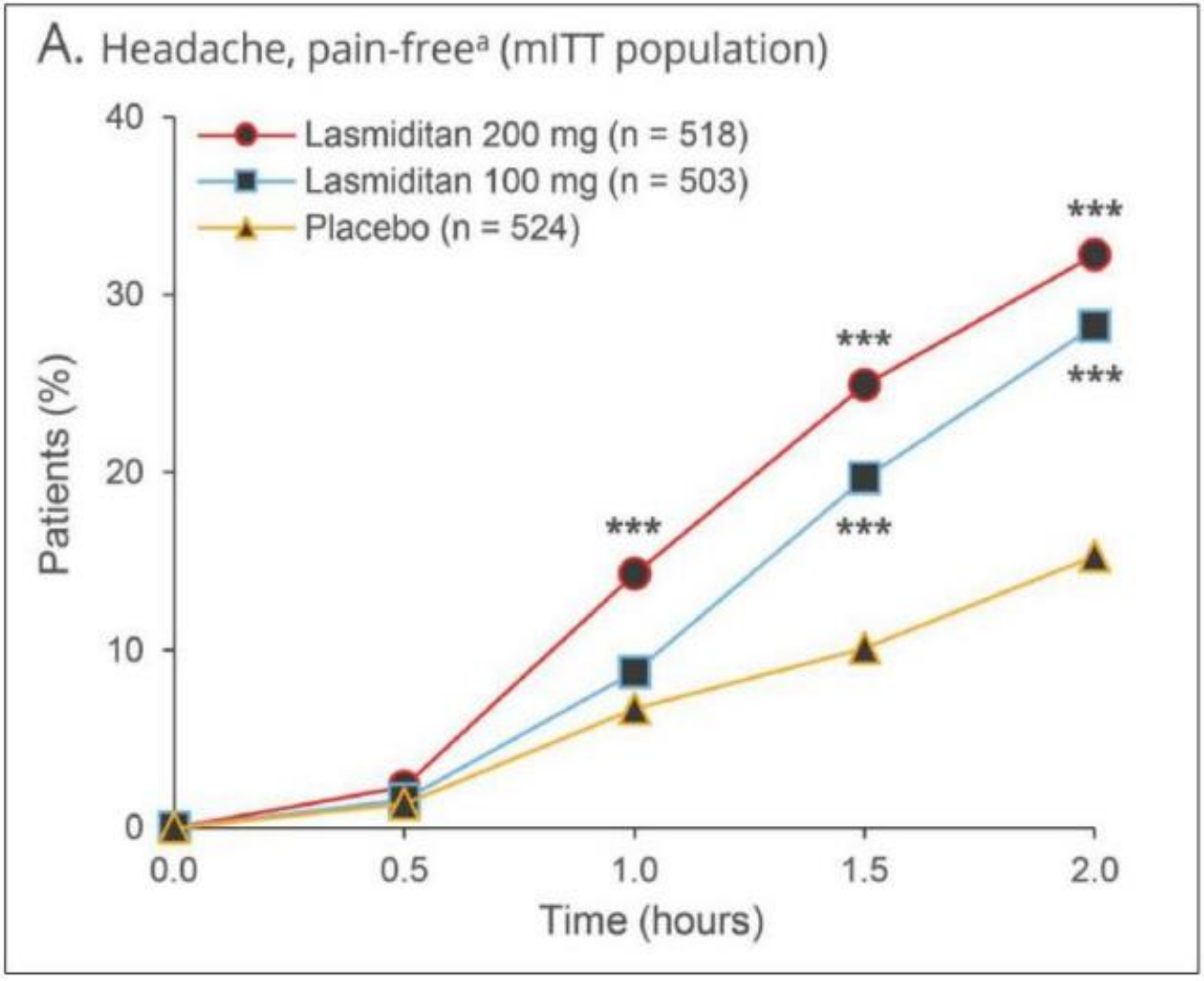

Side effects:

- Dizziness
- Fatigue
- Lethargy
- Nausea
- Paresthesia
- Somnolence

Gepants

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- Small molecule CGRP-RA don't cause vasoconstriction, thus no contraindication for vascular disease or those at risk
- First generation gepants studied over 16 years ago caused DILI-telcagepant. No issue with current 4th generation drugs now appoved
- Ubrogepant, Rimegepant and Atogepant are currently approved (vazegepant in trials)
- Similar efficacy, low side effects, but slower relief/ resolution of pain compared to triptans

Gepants

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- Ubrogepant 50mg and 100mg have 61% pain relief at 2hrs with side effects not above placebo;max 200mg/24hrs
- Rimegepant 75mgodt one/day, best empty stomach with 60% pain relief at 2hrs. Side effect of 2% nausea like placebo
- Rimegepant is now FDA approved as qod tab for episodic migraine prevention. It has a half life of 11hrs. Side effects are 2.7% nausea and 2.4% stomach pain

Gepants

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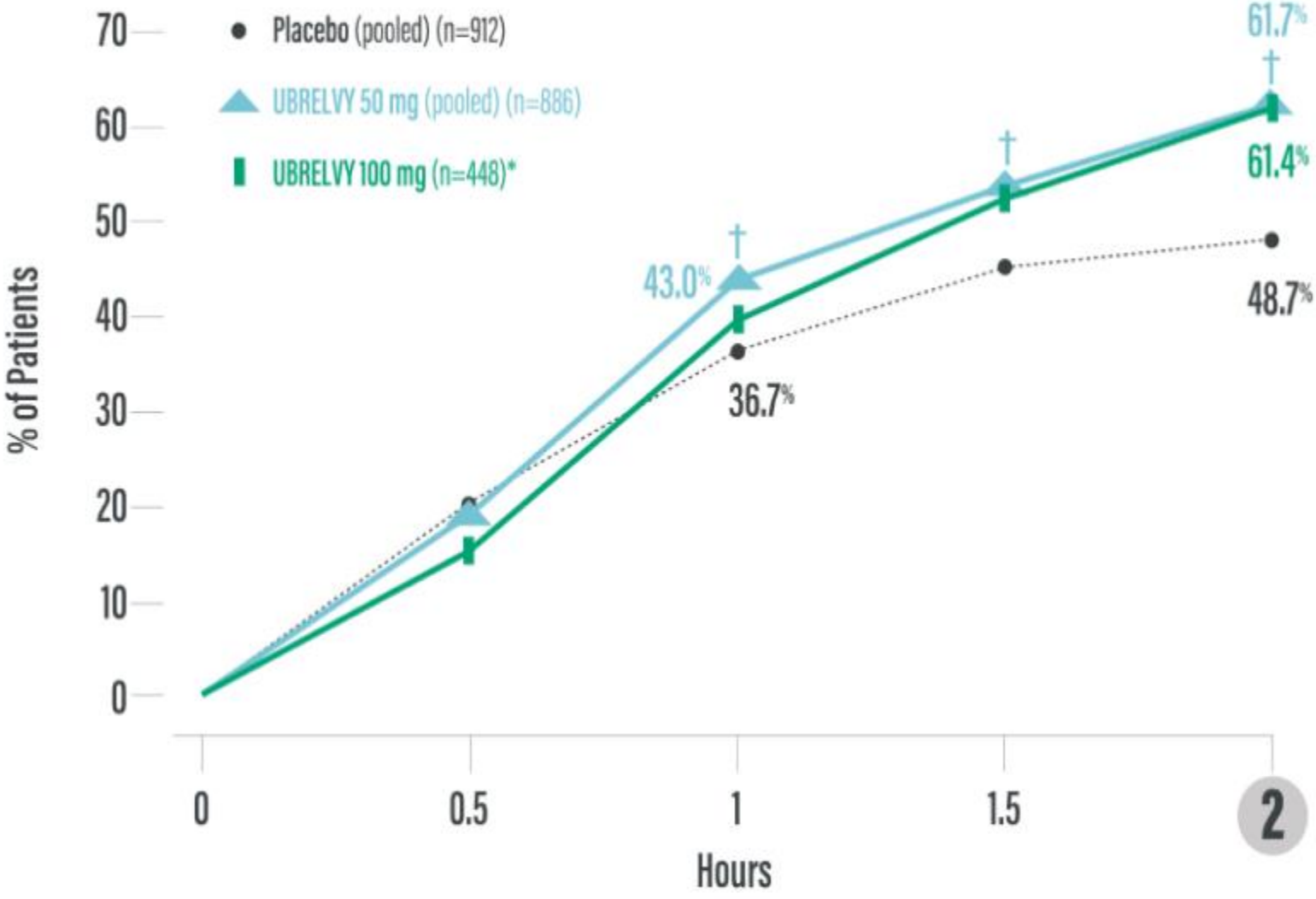
- Although in studies the gepants could not be taken until mod-severe pain which may reflect lower pain freedom at 2 hours.
- Ubrogepant and rimegepant act at same site and have pain freedom of about 20% at 2hours
- Metabolized by CYP3A4 so avoid antifungal meds and clarithromycin
- Use 50mg dose of ubrogepant if taking calan/ fluconazole /luvox/grapefruit juice

Pain relief at 2 hours—secondary endpoint[1]



Ubrogepant

Pain freedom

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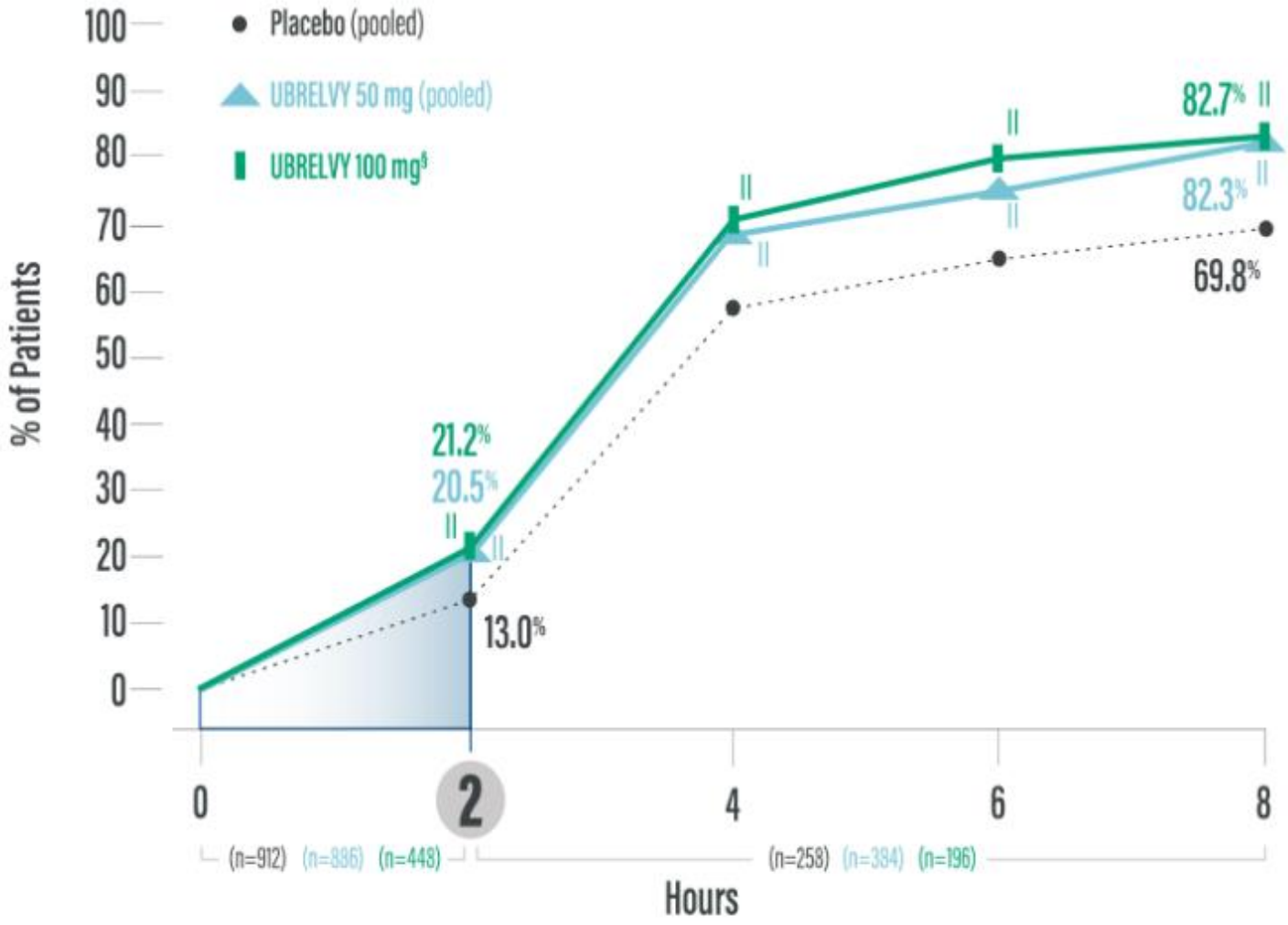
Pain freedom at 2 hours—co-primary endpoint[†‡]



Rimegepant

Pain relief

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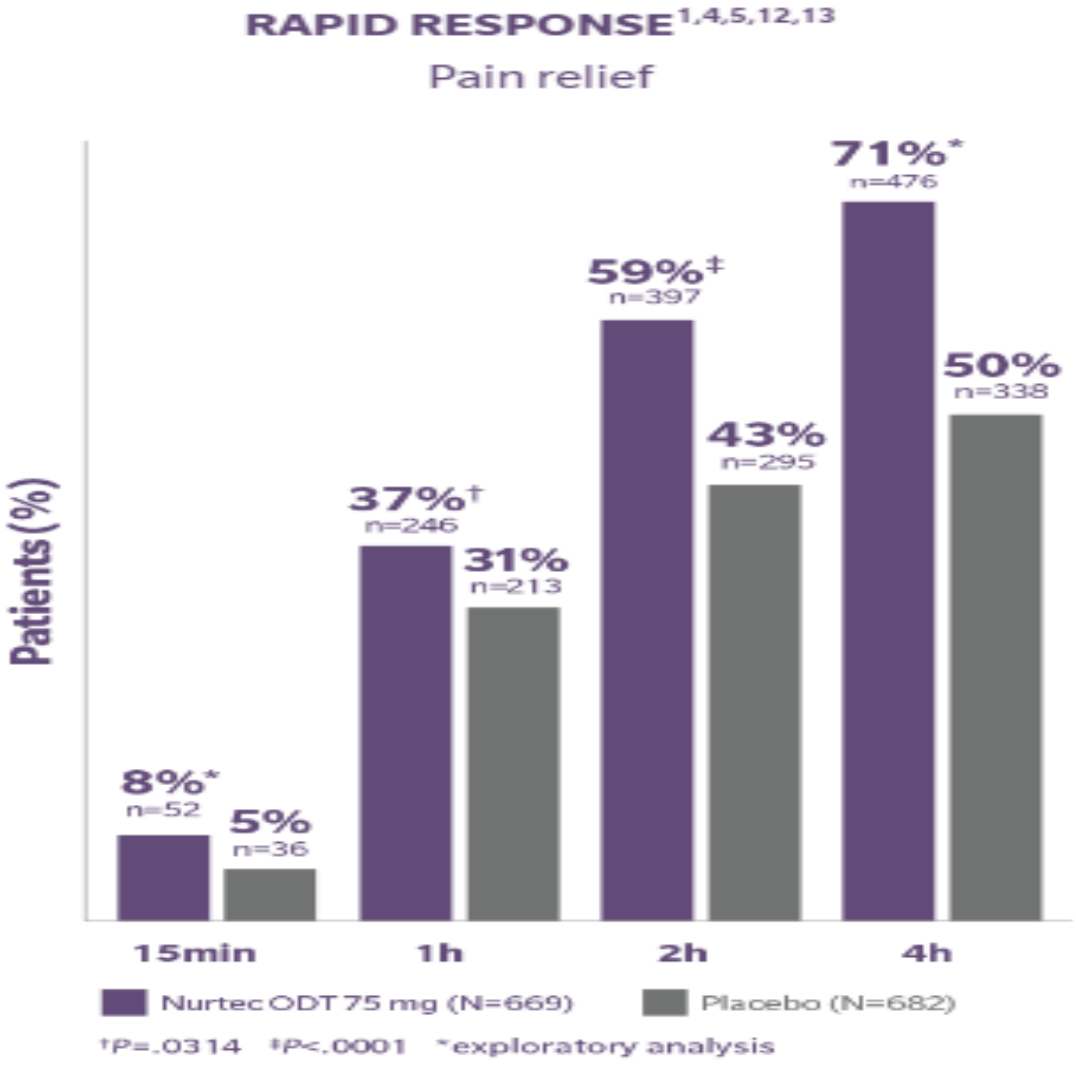

Rimegepant

Pain freedom

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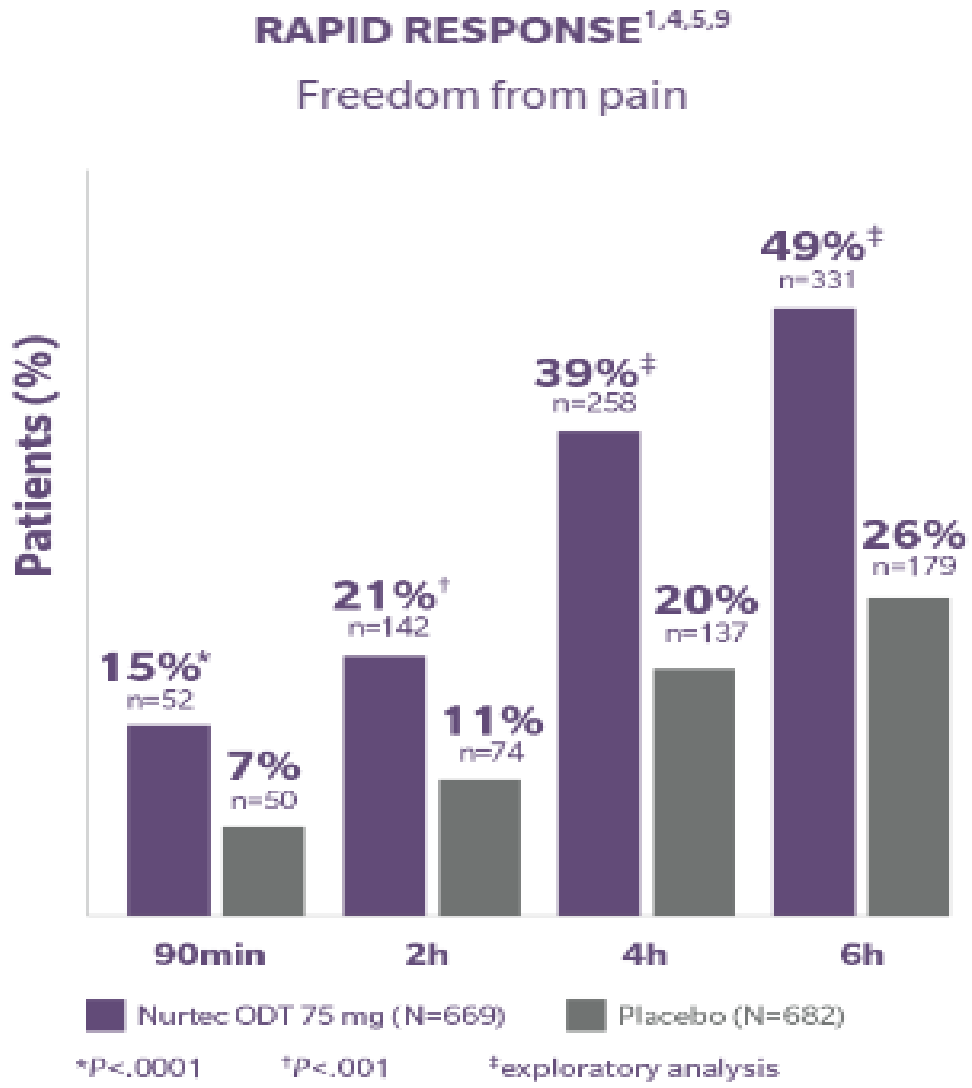

Atogepant/Qulipta

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- Atogepant/Qulipta also approved as a daily preventative for episodic migraine
- Side effects of 9% nausea, 6% constipation and fatigue at the 60mg dosage, but also has a 10mmg and 30mg dose
- Half life of 11 hours; Tmax 1-2 hours
- Decreased mean monthly migraine days by 54% vs 33% for placebo in a 3month trial of 60mg daily
- Drug interactions with CYP3A4 inhibitors i.e. ketoconazole, *clarithromycin etc*

Qulipta

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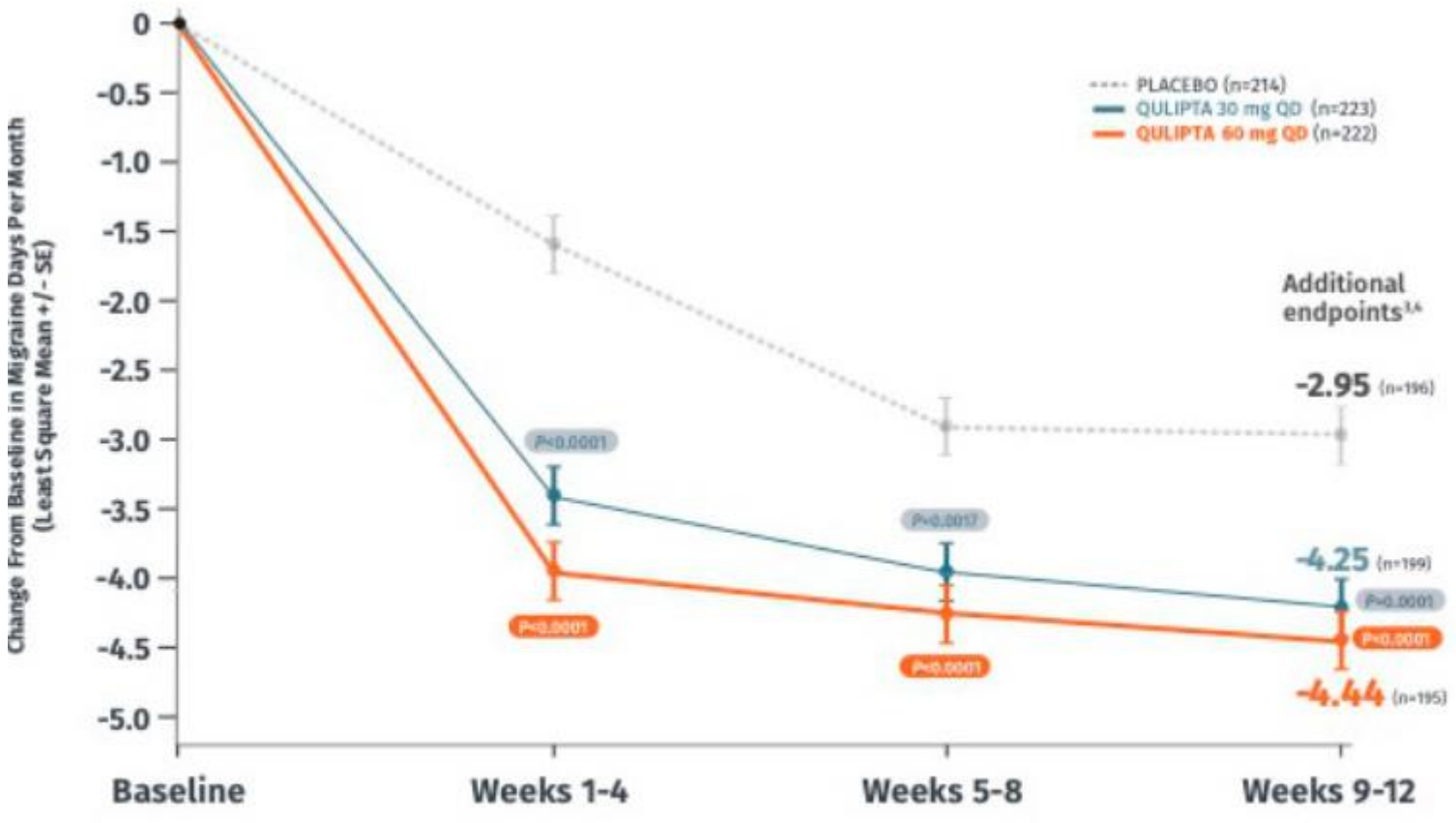

BASELINE MMD WAS, ON AVERAGE, 7.7.[1]

Trudhesa

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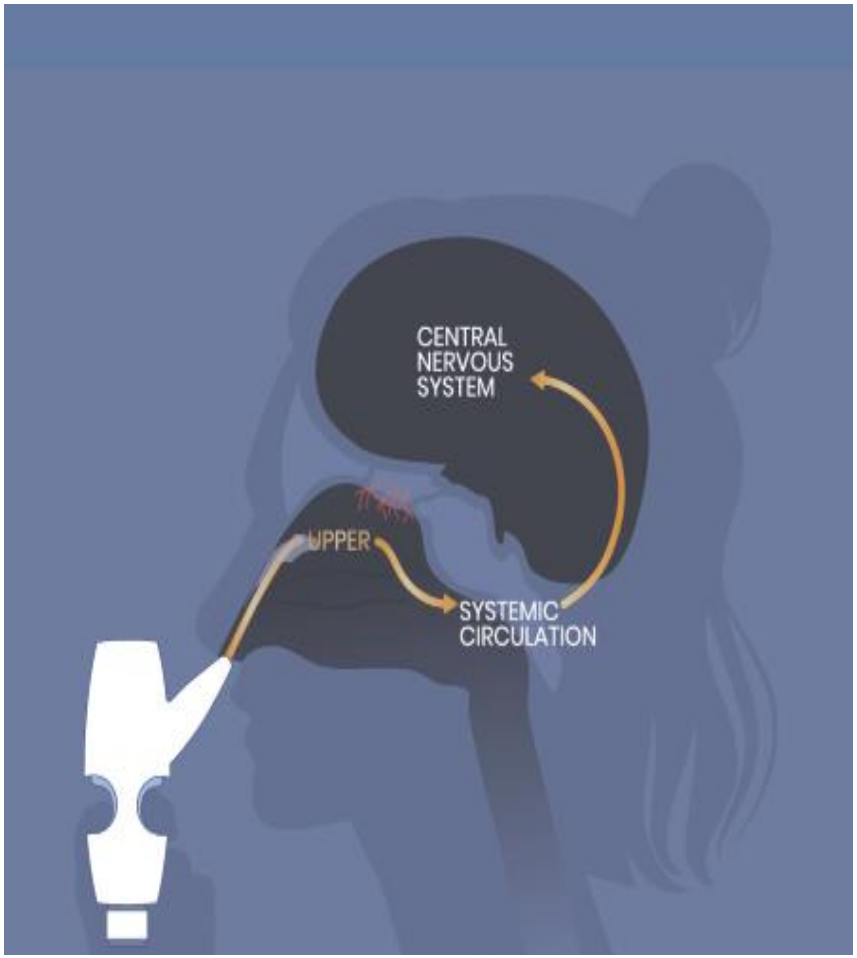

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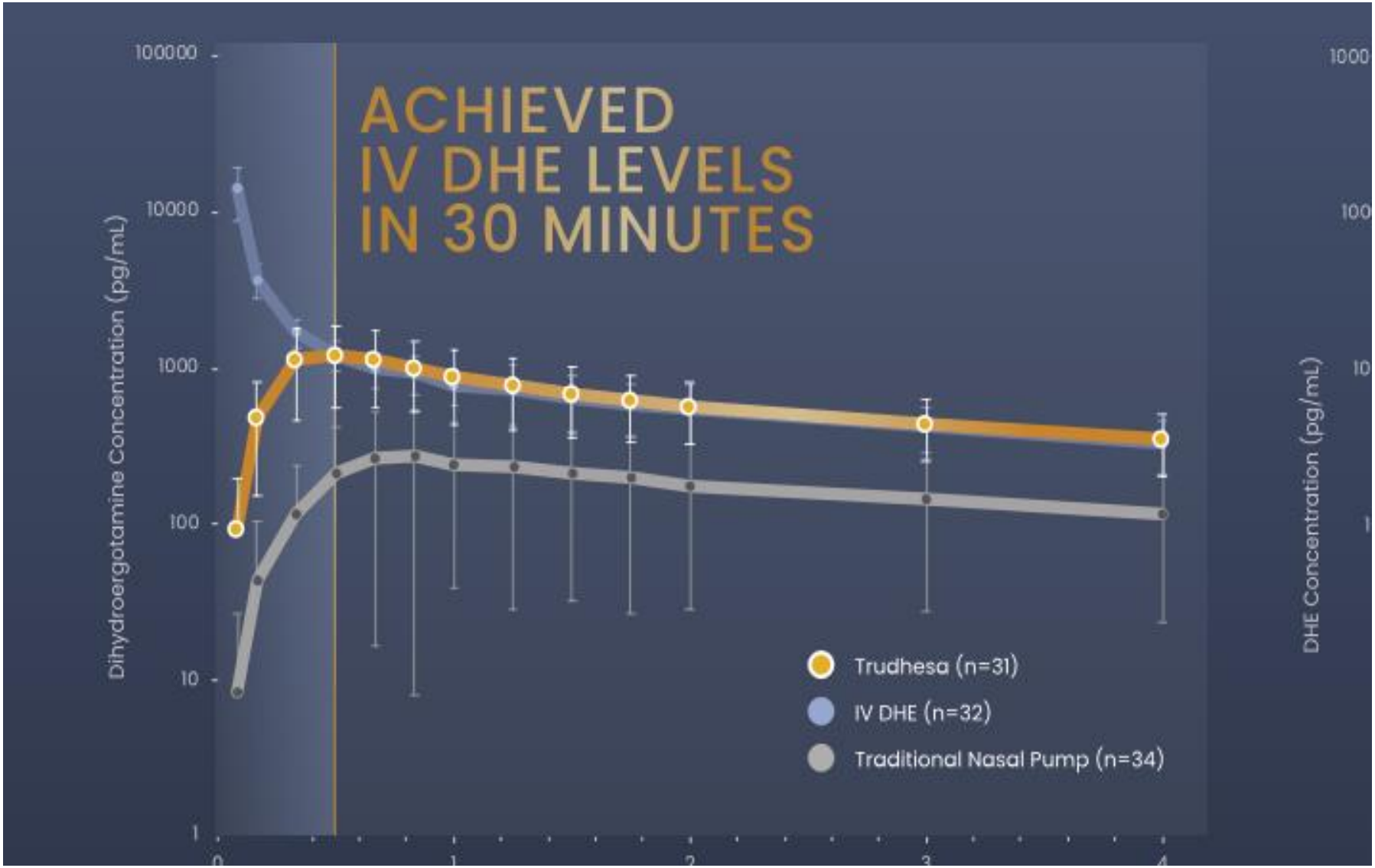

Pain relief post dose

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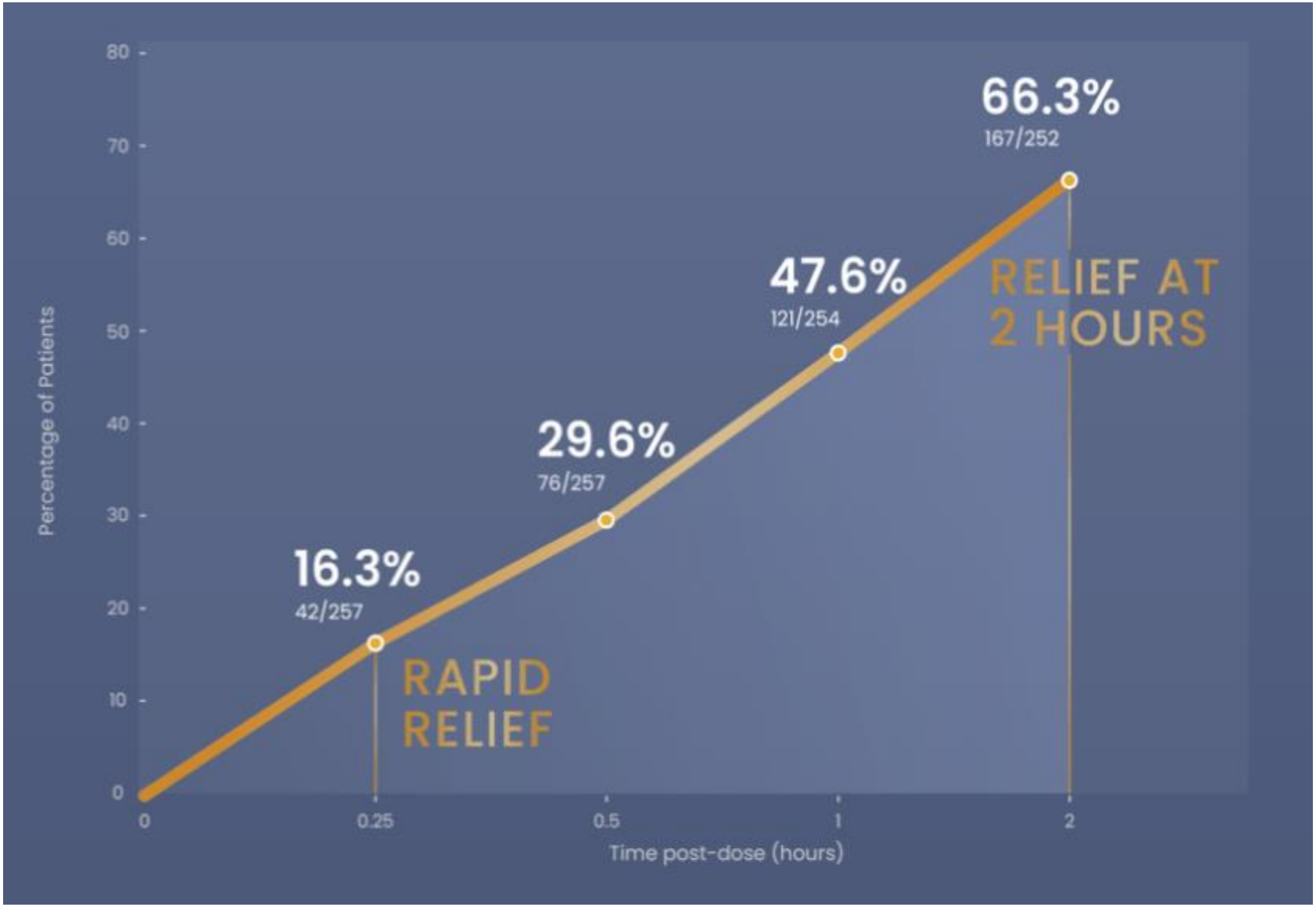

Elyxyb

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Elyxyb

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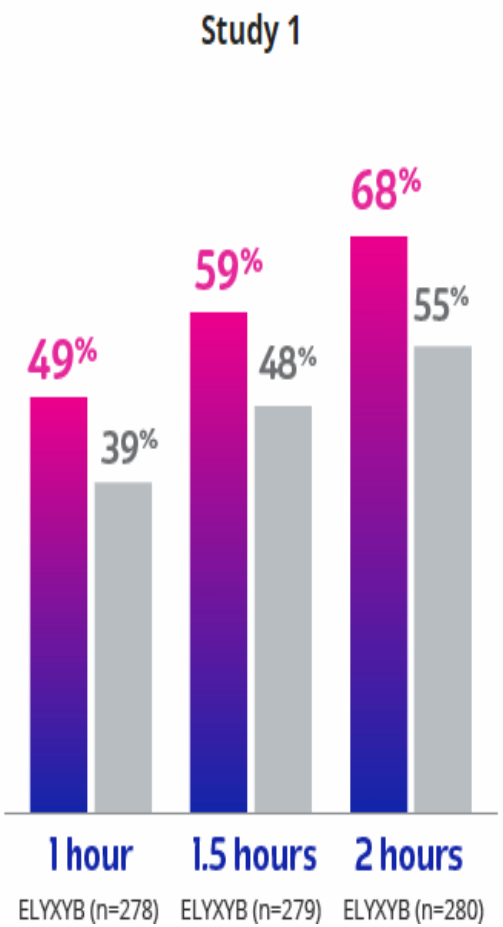
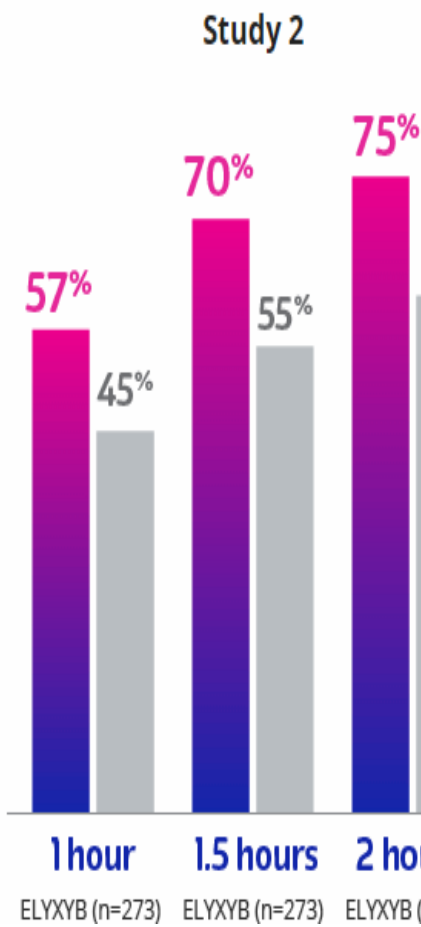
ADDITIONAL ENDPOINTS (POST HOC ANALYSIS)

Pain relief at 1, 1.5, and 2 hours[8,9]

ELYXYB Placebo





Elyxyb

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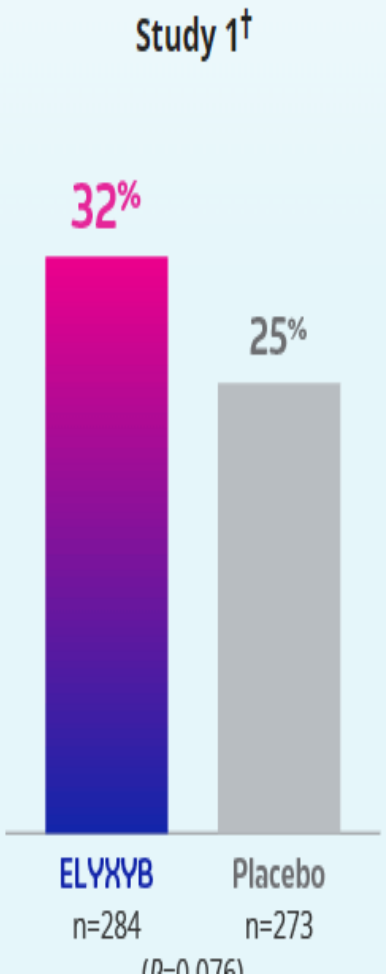
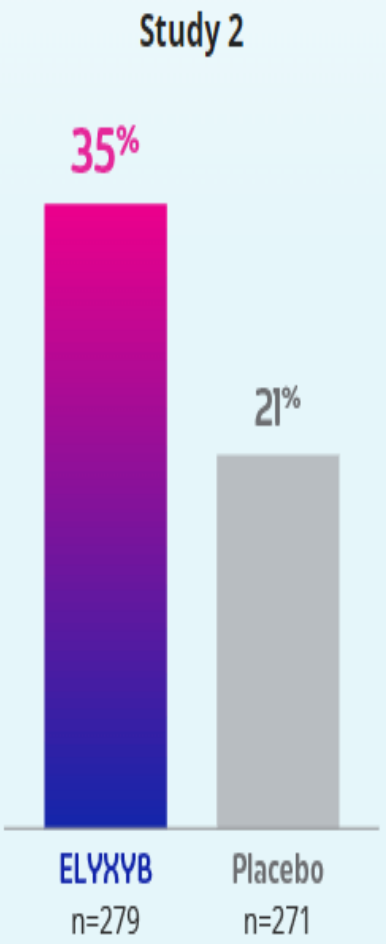
CO-PRIMARY ENDPOINTS: PAIN FREEDOM AND FREEDOM FROM MOST BOTHERSOME SYMPTOM (MBS) AT 2 HOURS

Pain freedom at 2 hours[5]





To sum it up

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Pain Freedom	2hrs	Pain Relief	2 hrs
• Reyvow	33-39%	• 61%	
• Ubrelvy/			
• Nurtec	20%	• 60%	
• Trudhesa	39%	• 66%	
• Elyxyb	32-35%	• 68-75%	

Initiation of prophylaxis

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- ≥ 3 mod or severe HA days/M that don't respond to acute meds consistently
- 6-8 HA days/M even if acute meds work
- Contraindications to acute meds
- Bothersome symptoms even if infrequent (hemiplegic migraine, migraine with brainstem aura)
- Migraine has significant impact on patient's life despite lifestyle modifications, trigger avoid, acute meds
- Pt is at risk of developing medication-overuse HA

Schwedt TJ. Preventive therapy of migraine. Continuum 2018;24:1052-1065.

mABS

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- Large molecules that antagonize CGRP at the receptor or ligand and do not cross the BBB
- No drug interactions noted as metabolism is by the reticuloendothelial system
- Show efficacy in treating EM (>4 headache days/month) and CM
- Relatively few side effects compared to prior prophylactics

mAbs and episodic migraine

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AHS indications for initiating tx with CGRP mAbs in episodic migraine

Use is approved when all of the following are met:

- Prescribed by a licensed medical provider who is authorized to practice and performing within the scope of practice
- Pt is at least 18 years of age
- Diagnosis of ICHD-3 episodic migraine with or w/o aura (4-7 MHDs) and **both of the following**:
  - Inability to tolerate (due to side effects) or inadequate response to a 6-wk trial of at least 2 of the following:
    - Topiramate
    - Divaloproex sodium/valproate sodium
    - Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
    - Tricyclic antidepressant: amitriptyline, nortriptyline
    - Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
    - Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
  - At least moderate disability (MIDAS>11, HIT-6>50)

The American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache 2019;59:1-18.

mAbs and chronic migraine

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AHS indications for initiating tx with CGRP mAbs in chronic migraine

Use is approved when all of the following are met:

- Prescribed by a licensed medical provider who is authorized to practice and performing within the scope of practice
- Pt is at least 18 years of age
- Diagnosis of ICHD-3 chronic migraine and **either of the following**:
  - Inability to tolerate (due to side effects) or inadequate response to a 6-wk trial of at least 2 of the following:
    - Topiramate
    - Divaloproex sodium/valproate sodium
    - Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
    - Tricyclic antidepressant: amitriptyline, nortriptyline
    - Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
    - Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
  - Inability to tolerate or inadequate response to a minimum of 2 quarterly injections (6 months) of onabotulinumtoxinA

The American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache 2019;59:1-18.

mAbs

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MAB treatment when the patient has EM reduces mean monthly migraine days with greater responder rates than any previous preventive treatment, and thus prevents progression to CM

MAB treatment when the patient has EM and acute medication use ≥10 days per month, thus putting them at risk for MOH, is reversed by the MABs, and thus prevents progression to MOH

MAB treatment when the patient has CM and MOH is more likely than not to convert the patient to EM and no medication overuse, *without further intervention*

These changes occur with overuse of analgesics, combination analgesics, and triptans, unlike with onabotulinumtoxinA, which only reduced triptan overuse in the regulatory CM/MOH trials

However, patients overusing narcotics or barbiturates were excluded from the MAB trials

Onabotulinum

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- Botox A blocks CGRP release from meningeal and extracranial c fibers
- Botox A is internalized in the afferent nerve terminals and cleaves SNARE, therefore synaptic vesicles cannot attach to the membrane and inhibits neuropeptide release and insertion of new receptors. This blocks CGRP glutamate and substance P
- In humans the anti-nociceptive mechanism of the toxin has been studied with intradermal injections of capsaicin.

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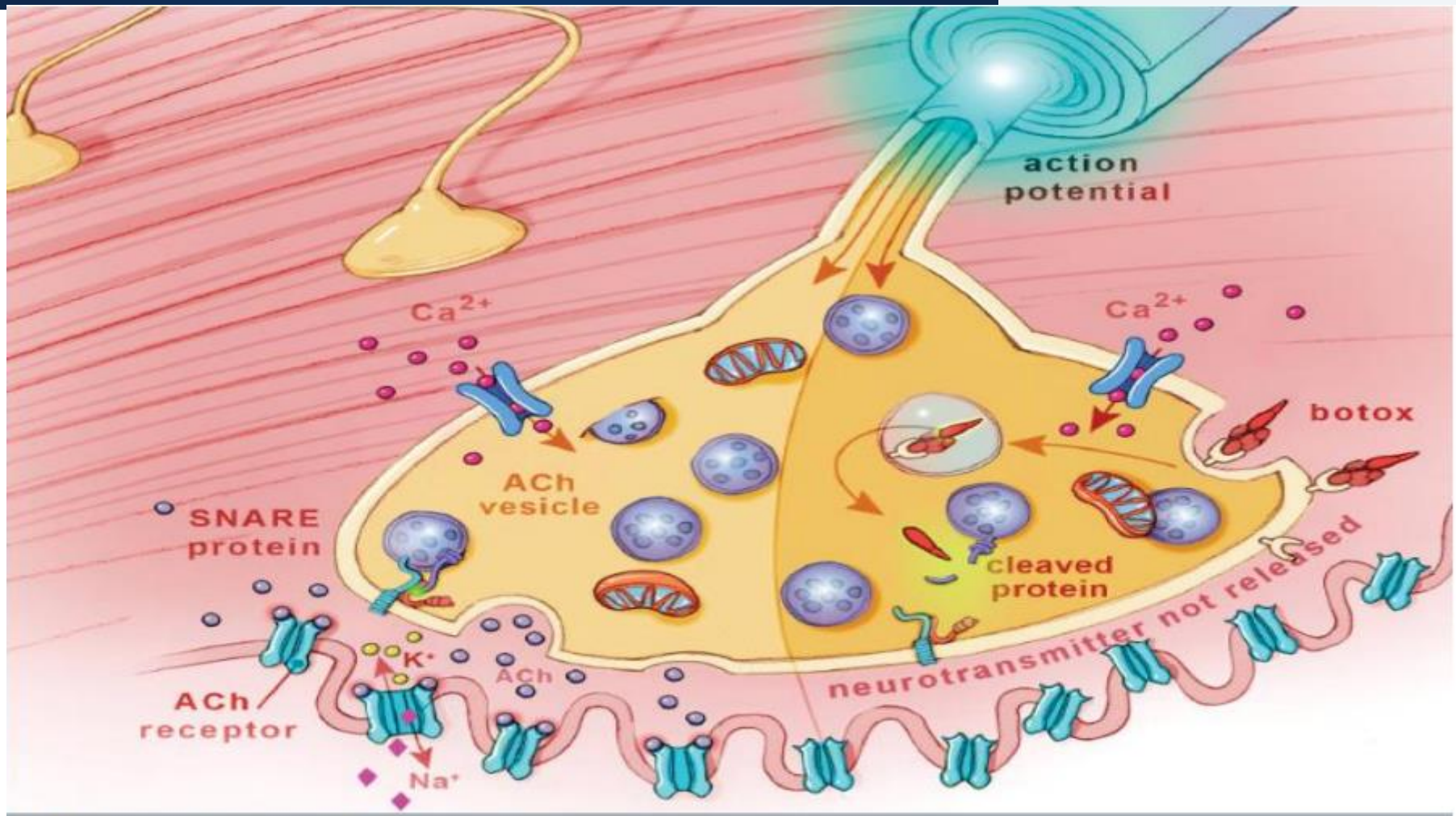

Mechanism of action of Botulinum toxin:

Botox interferes with SNARE proteins. This blocks the vesicle where Acetylcholine (ACh) is stored from binding to the membrane; inhibiting the release of the neurotransmitter from the neuron.

Injection sites onabot

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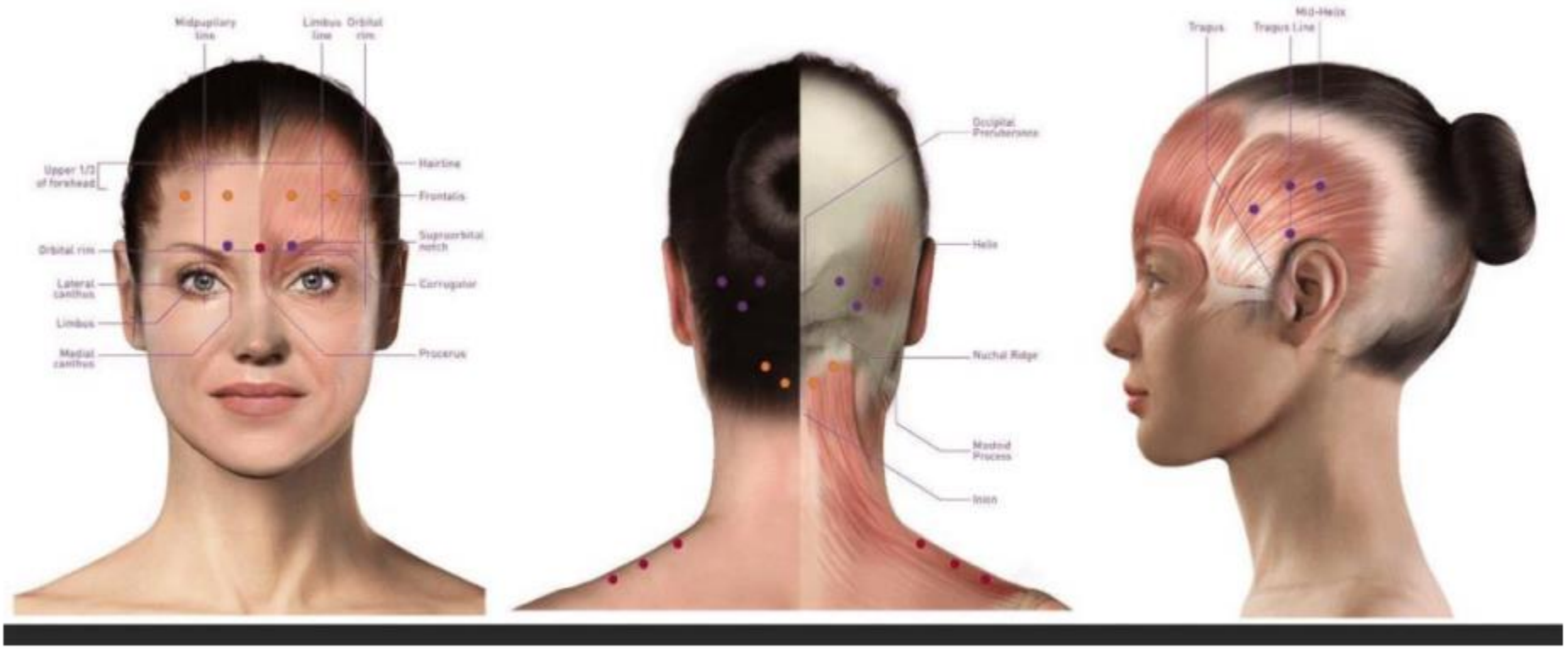

Nerivio

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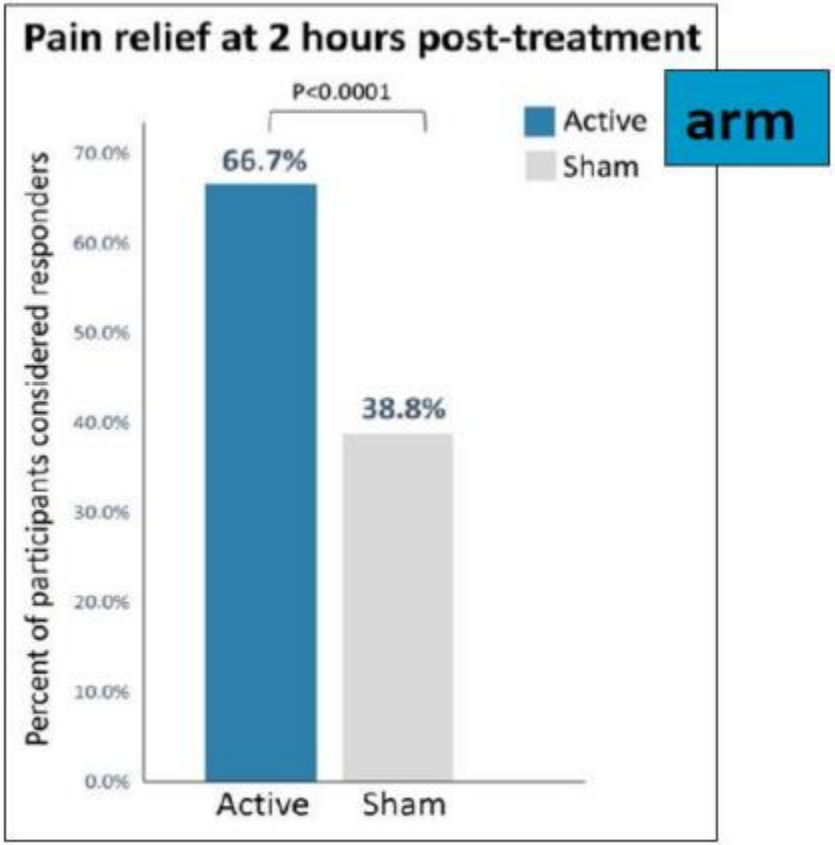
- Emerging alternative for acute treatment of migraine with better efficacy than other neuromodulation devices.
- Stimulates upper arm peripheral nerves, median and musculocutaneous, to induce conditioned pain modulation(CPM)- a descending endogenous analgesic mechanism in which subthreshld conditioning stimulation inhibits pain in remote body regions.

- Nerivio Migra arm patch



theranica.com

- Presumably activates inhibition pathways from periaqueductal gray, RVM and involve release of serotonin, noradrenalin to inhibit incoming pain messages in the TCC
- 296 patients in pivotal study, 2-8 ha days/month and use was determined at 45min. Less pain relief if not used within first 20min. Safety profile is good with pain relief of 66.7% at 2 hrs, and pain freedom of 37.4%, 2hrs

REN

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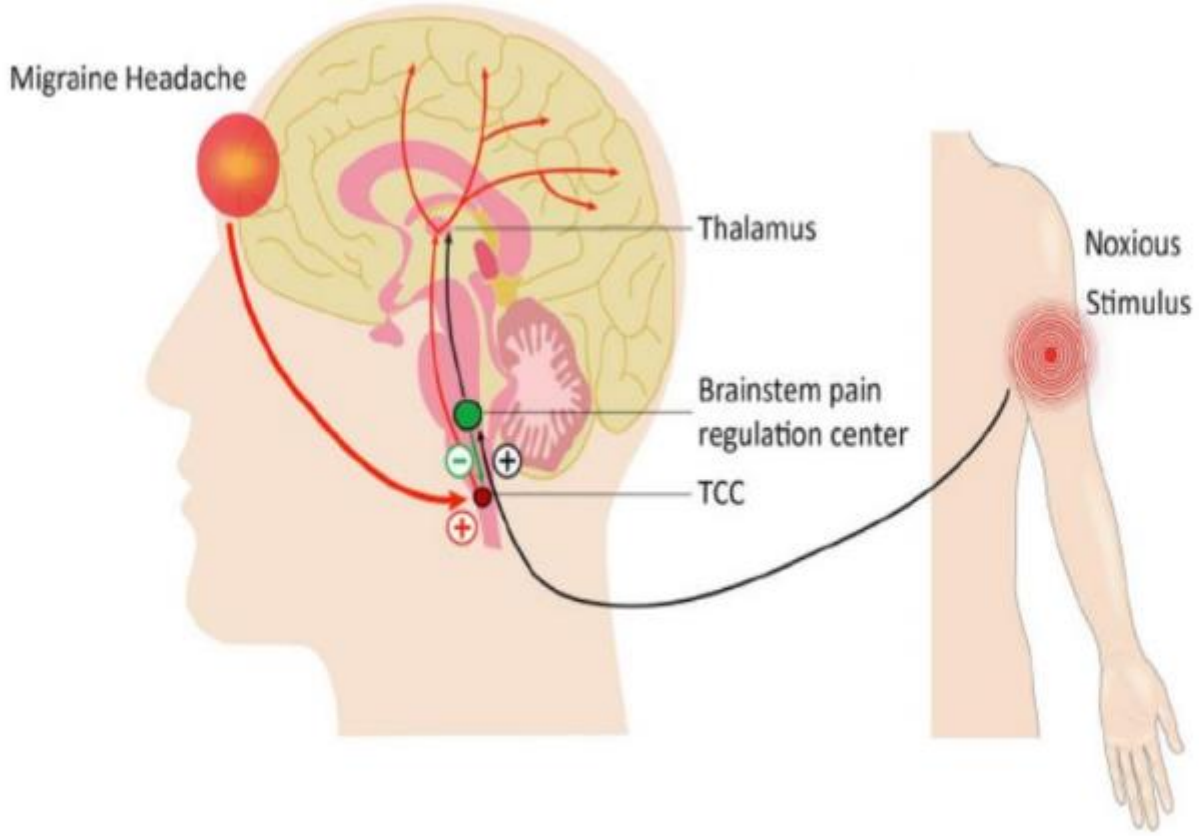

Relivion

- Combination occipital and trigeminal neurostimulation system that applies a mild electrical impulse to 6 nerve branches
- FDA approved currently for acute migraine only

Relivion

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- New data presented at recent AHS annual meeting regarding relivion as a preventative treatment
- No approval yet

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- References upon request

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