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DISCLOSURES

All: Allergan-Abbvie, Novartis,Teva, AZ, GSK, MSD, NycoMed, Organon, Pfizer, Lundbeck, Eli Lilly

Relevant disclosures: Allergan-Abbvie, Novartis,Teva, Lundbeck, Eli Lilly

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COMBINATION THERAPY AND SWITCHING

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AGENDA

- Why combining profylactic medication?
- Why switching?
- Lock-and-key analogy
- The consultation
- Different scenarios
- How to define clinical effectiveness of migraine preventive drugs
- What does the literature say so far?

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- One of the most important goals in managing migraine is to prevent episodic migraine from transforming into chronic migraine
- Yet we don’t start injectable preventive treatment until the patient presents with a chronic migraine
- Improved management would be of benefit for both patients and society

Migraine "The forgotten Epidemic" Rome 2005

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WHY?

- Oral preventatives are “borrowed” from other medical conditions. Few are proven effective on chronic migraine
- The CGRP pathway medications are designed to help prevent or treat migraine
- They may work well for some patients and not for others
- There are inter-individual differences in response to a given preventative
- For some patients preventive medications work well, but not optimal – they are still suffering from severe attacks and switching or combination therapy may be necessary

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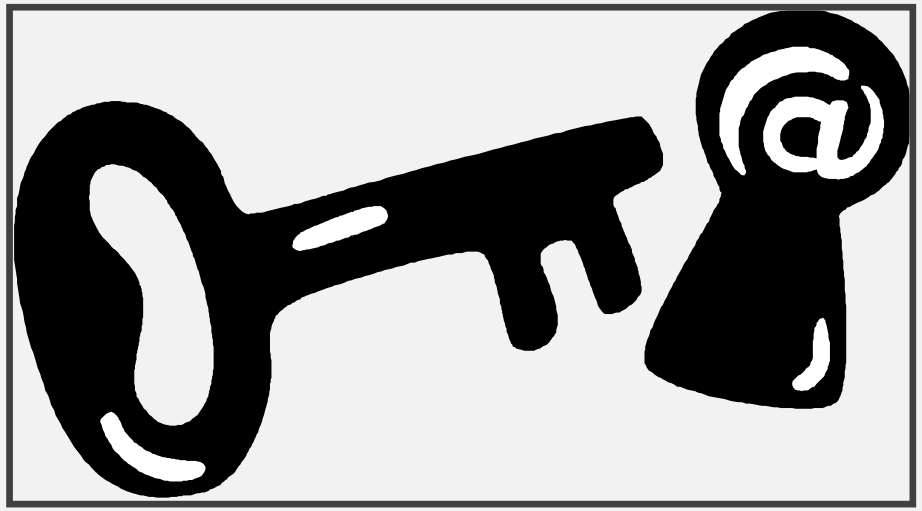
LOCK-AND-KEY ANALOGY

- The monoclonal antibodies target the CGRP pathway
- They work by binding to CGRP peptide (ligand) or its receptors
- The **lock-and-key analogy** helps explain how these drugs disrupt the CGRP process
- The CGRP peptide act as the key and the receptor acts as the lock



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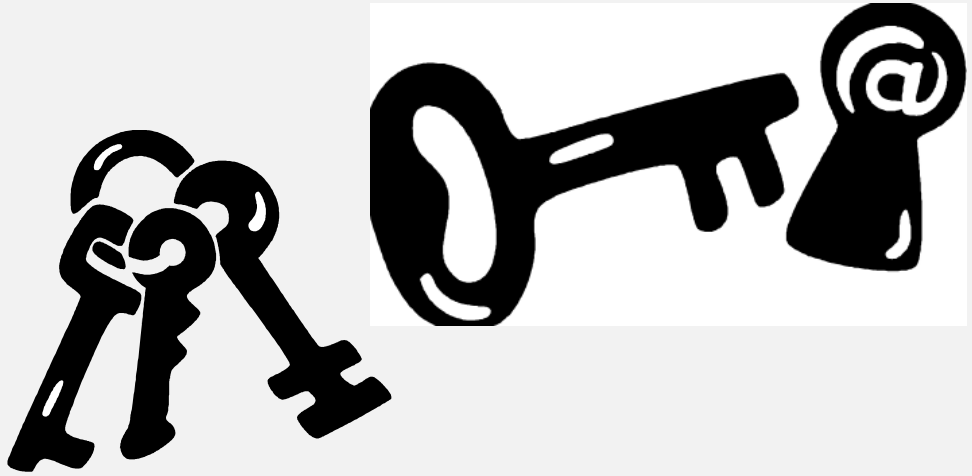
DIFFERENT MECHANISMS

- Aimovig blocks the lock, which allows less of the CGRP peptide to bind to the receptors, preventing activation

- Ajovy, Emgality, and Vyepti attach to the key, binding to it, preventing it from activating CGRP receptors



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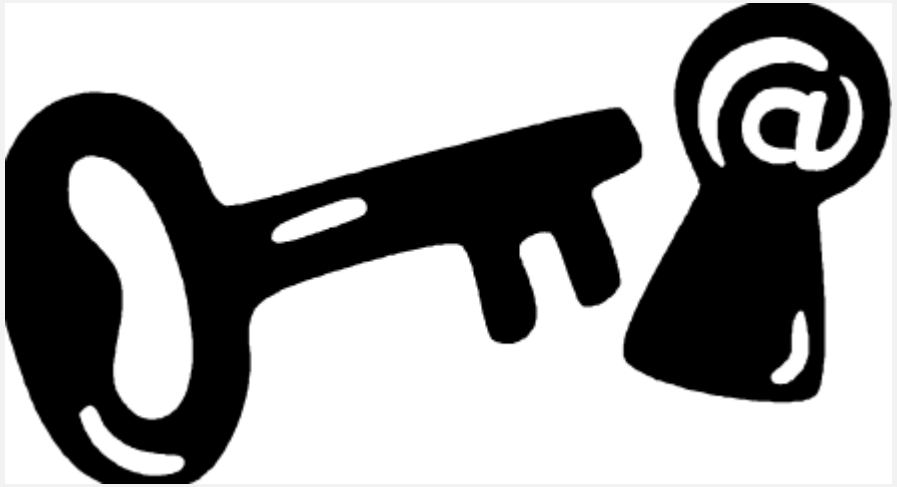

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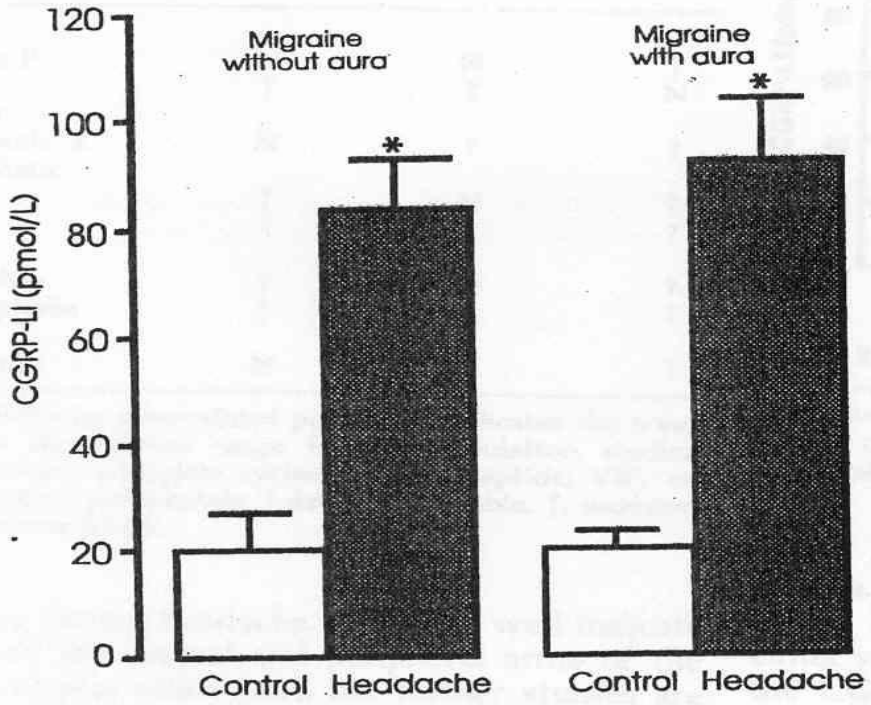

Fig. 2. Changes in CGRP levels during migraine headache. Open bars represent control measurements taken from external jugular vein (EJV); filled bars represent measurements from EJV taken during migraine attacks. An asterisk indicates that there is a significant difference between that measurement and the control. Values represent means ± SEM, $n = 10-22$.

Edvinsson L, Goadsby PJ.
Cephalalgia 1994;14:320-7

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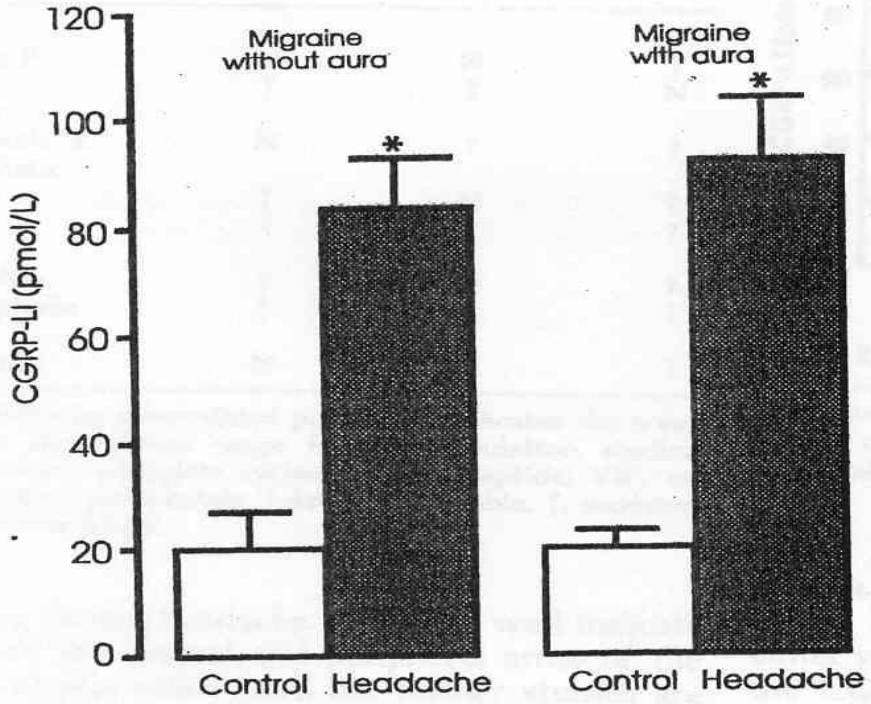

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Picture from Roger Cady

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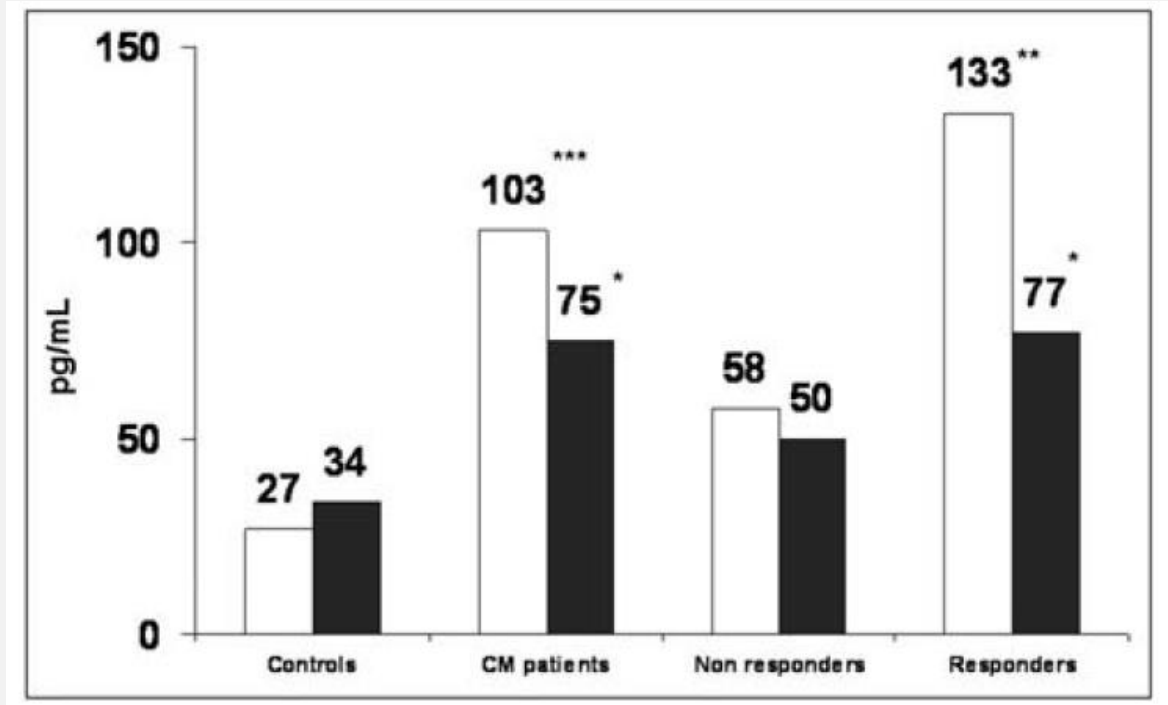
AN EXPLANATORY MODEL

Migraine patients are having a higher level of CGRP than people without this brain disorder?



Ramon et al. Curr Opin Neurol 2017 Jun;30(3):281-286

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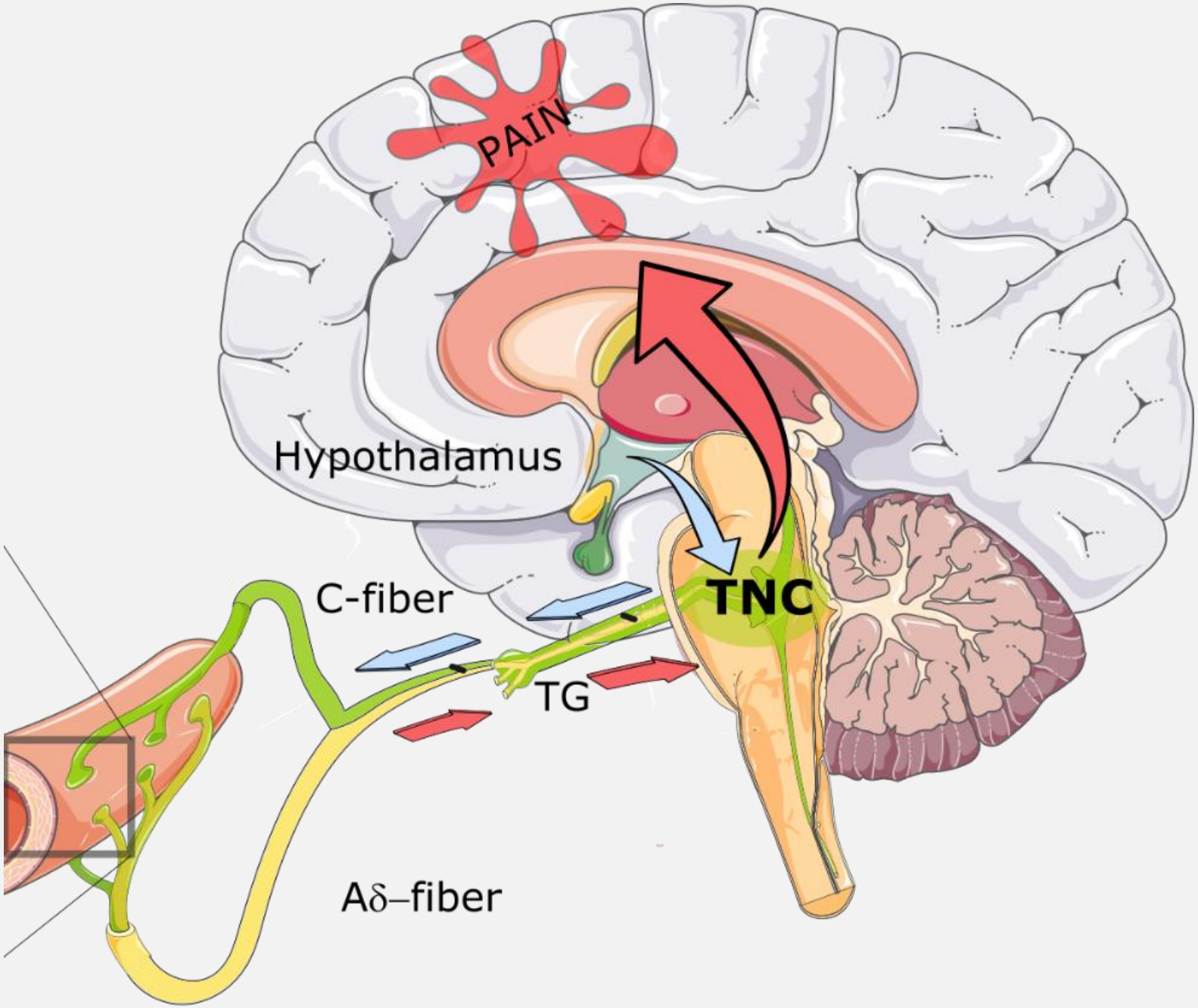
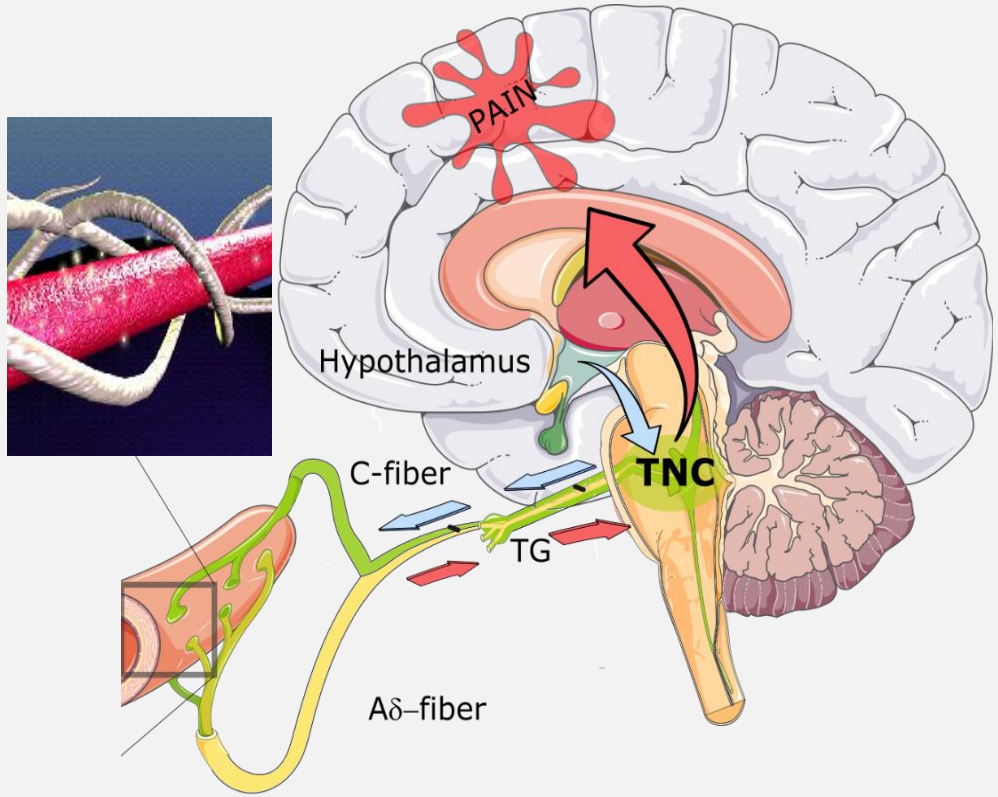


Haanes and Edvinsson, 2019
CNS Drugs

- The CGRP is among others found in the thinly myelinated (Aδ) and unmyelinated (C) fibers
- It is suggested that the CGRP targeted mAbs act primarily on the **Aδ-fibers**, and not the C-fibers
- Current theories suggest that Onabotulinumtoxin A also act as an inhibition of the CGRP pathways, probably mediated through the **C-fibers** more than Aδ-fibers



Haanes and Edvinsson, 2019
CNS Drugs

MIGRAINE TREATMENT TARGET: CGRP

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Triptans & ergots prevent CGRP release

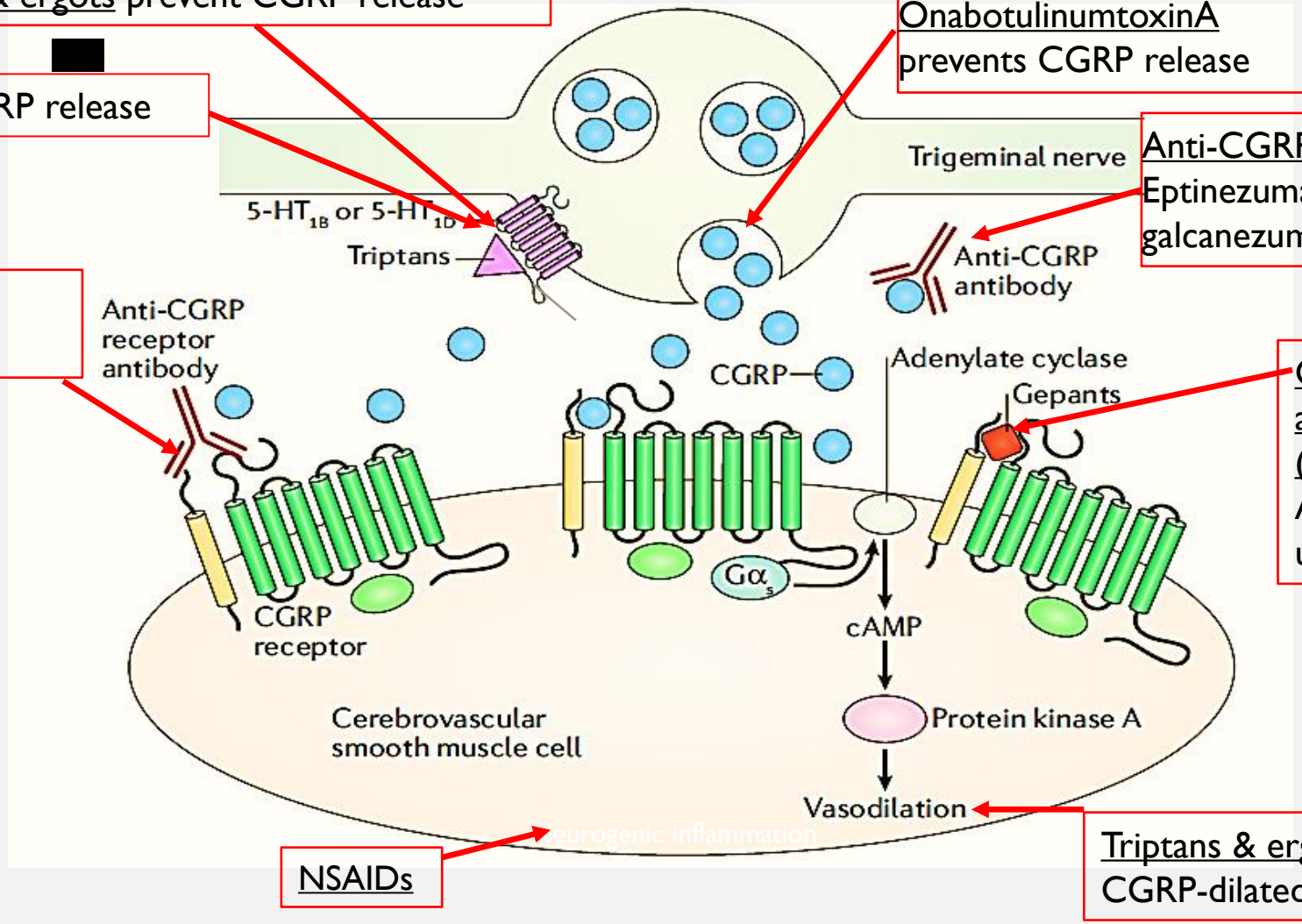
Lasmiditan prevents CGRP release

OnabotulinumtoxinA prevents CGRP release

Anti-CGRP ligand mAbs: Eptinezumab, fremanezumab, galcanezumab

Anti-CGRP receptor mAb: Erenumab

CGRP receptor antagonists (gepants) Atogepant*, rimegepant, ubrogepant, zavegepant*



*Investigational

NSAIDs

Triptans & ergots constrict CGRP-dilated vessels

Adapted from Edvinsson et al. *Nat Rev Neurol.* 2018;14:338-350.

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THE CONSULTATION

Patient expectations

Follow up consultations

Headache diary

Stop in time

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Follow up consultations

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Stop in time

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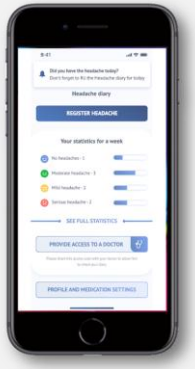

Headache diary

Stop in time

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DIFFERENT SCENARIOS

CHRONIC MIGRAINE PATIENT

Has tried at least 3 different oral profylactic medications – lack of effect or side effects

1)Has been treated with Botox – didn't work

- side effects

- partly worked

2) Has not been treated with Botox

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DIFFERENT SCENARIOS

CHRONIC MIGRAINE PATIENT

Has tried at least 3 differet oral profylactic medications – lack of effect or side effects

1) Has been treated with Botox – didn't work

- side effects

- partly worked

CGRP AB

2) Has not been treated with Botox

CGRP AB or BOTOX

HOW TO DEFINE CLINICAL EFFECTIVENESS OF MIGRAINE PREVENTIVE DRUGS

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The 2 most important factors that lead to the decision of continuing preventive drug treatment;

1) Objective – reduction in use of acute migraine treatment medication
2) Subjective – positive patient perception of treatmenmt effectiveness

Intensity
Duration
Frequency
Impact

Pozo- Rosich et al. (2021). My- LIFE European Delphi survey. European Journal of Pain, 25, 2177– 2189.

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DIFFERENT SCENARIOS

- Absolutely no effect of a mAb
- Absolutely no effect BOTOX

- Partly effect a mAb
- Partly effect BOTOX

- Side effect of a mAb
- Side effect of Botox

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WHAT WOULD YOU DO?

- Absolutely no effect of a mAb
- Absolutely no effect BOTOX

- Partly effect a mAb
- Partly effect BOTOX

- Side effect of a mAb
- Side effect of Botox

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WHAT WOULD I DO?

- Absolutely no effect of a mAb
- Absolutely no effect BOTOX

SWITCH OT TRY BOTOX

TRY mAbs

- Partly effect of a mAb
- Partly effect BOTOX

ADD BTX OR SWITCH

ADD mAbs

- Side effect of a mAb
- Side effect of Botox

SWITCH after pause or BOTOX

mAbs

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FOR HOW LONG?

- Absolutely no effect of a mAb
- Absolutely no effect BOTOX

3

SWITCH OT TRY BOTOX

TRY mAbs

- Partly effect of a mAb
- Partly effect BOTOX

6

ADD BTX OR SWITCH

ADD mAbs

- Side effect of a mAb
- Side effect of Botox

0

SWITCH after pause or BOTOX

mAbs

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WHAT DOES THE LITTERATURE SAY?

4 real-world evidence studies looking at Chronic Migraine patients receiving CGRP mAb therapy added to Onabotulinumtoxin A

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- Retrospective chart reviews:
- 257 patients *1
- 78 patients *2
- 153 patients *3
- Case series: 17 patients *4

RESULTS

Favorable outcomes with combination therapy

Adding a CGRP-targeted mAb to Botox in patients with CM was associated with further reductions in MHDs and MMDs as well as reduced headache severety

No major tolerability issues across a range of mAbs (erenumab, fremanezumab and galcanezumab)

1*A Blumenfeld et al (2021) Real-Worl evidence for control of Chronic migraine patients receiving CGRP mAb therapy added OnabotulinumtoxinA; a retrospective chart review. Pain and therapy.

2* Mark Armanious ,et al (2020): Erenumab and OnabotulinumtoxinA Combination Therapy for the Prevention of Intractable Chronic Migraine without Aura: A Retrospective Analysis, Journal of Pain & Palliative Care Pharmacotherapy, DOI: 10.1080/15360288.2020.1829249

4* Fred Cohen MD1 et al (2021) Efficacy and tolerability of CGRP targeted mAb medications as add-on therapy to Onabotulinumtoxin A in patients with Chronic migraine, Pain Medicine 22(8)p.1857-63

3* Tahlia Toni et al (2021) Effectiveness of dual migraine therapy with C
GRP inhibitors and OnabotulinumtoxinA injevtions: case seriesNeurological Sciences https://doi.org/10.1007/s10072-021-05547-x

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SUMMARY

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- Combination therapy for patients with severe CM, actually can decrease the frequency and severity of migraine attacks
- A combination therapy of BTX A mediation through the C-fibers and the mAbs through the Aδ-fibers may provide a synergistic effect on inhibiting the trigeminal nociceptive pathway
- Personally, I do both - switching therapy of the mAbs and combination therapy with mAbs and BTX A
- Real world retrospective studies on this combination therapy have been performed, and shown good outcome, safety and tolerability
- Randomized control trials are needed to further guide clinical practice

TAKE HOME MESSAGE

- Most migraine patients can be well treated and live a “normal life”
- Optimize their treatment
- Switch and/or combination of prophylactic medications may be needed and helpful for some of your patients