Practical Updates in Migraine

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Disclosures

- Advisory Boards/Speaker
  - Abbvie
  - Axsome
  - Pfizer

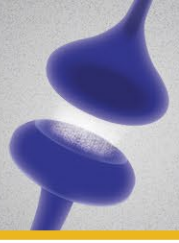
Learning Objectives

- Describe recent advances in Migraine Medicine
- Discuss new indications and emerging targets
- Understand the gut-migraine axis
- Apply new knowledge to clinical practice

New Era

- We are in a “new era” in headache medicine
- More biologically grounded mechanisms
- A shift from treating single attacks to managing migraine as a disease
- A disease that involves much more than head pain

New Era



- Expanding therapeutic targets beyond CGRP
- Rational combination strategies for non-responders
- Growing interest in sex-specific differences
- Evolving clinical paradigms (telehealth, digital tools, precision approaches)

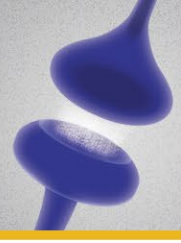
Fitzek MP, Boucherie DM, de Vries T, Handtmann C, Fathi H, Raffaelli B, MaassenVanDenBrink A.
J Headache Pain. 2025 Jan 3;26(1):3.

Headache Classification

- Refine headache classification so it better matches real-world patient phenotypes and supports better trials
- Ongoing debate on the boundary between episodic vs chronic migraine, especially the clinical “cliff” at 15 headache days/month (with ≥8 migraine-like days) and how to classify patients just below that threshold
- Menstrual migraine/perimenstrual headache is described as a major unmet need that still sits in the “appendix,” raising questions about whether emerging hormonally relevant mechanisms should drive reclassification
- Labeling headaches as primary vs secondary (post-traumatic headache with migraine phenotype) and how terminology like “medication overuse headache” can create stigma and confusion for patients

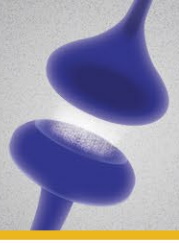
Holm A, Edvinsson JCA, Krause DN, Edvinsson L. J Headache Pain. 2025 Jun 17;26(1):142. doi: 10.1186/s10194-025-02071-7

Migraine Biomarkers and Predictability



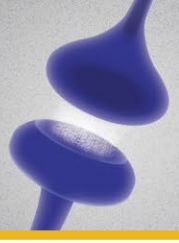
- Research aimed to enhance understanding of migraine pathophysiology
- This could lead to improved treatment strategies
- Can we predict migraine attacks?
- Can we determine response to treatment?
  - What are the factors that predict response?
- Can we “image” migraine?

Negative Predictors of Treatment Response



- Clinical features such as depression and allodynia are identified as negative predictors for treatment response
- This is particularly true for monoclonal antibody treatments
- Patients with depressive symptoms or hypersensitivity during migraine attacks are less likely to respond to these therapies

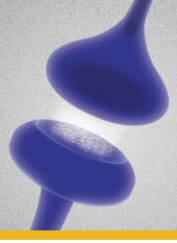
Psychological Factors and Behavioral Therapy



- Psychological factors:
  - pain catastrophizing and locus of control, influence treatment outcomes
  - Patients who catastrophize their pain are more likely to benefit from behavioral therapy
  - Incorporating behavioral treatments alongside medication can improve outcomes, especially when addressing comorbid conditions like depression.

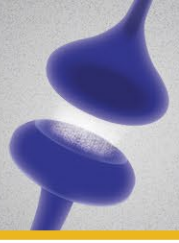
- Pelzer N, de Boer I, van den Maagdenberg AMJM, Terwindt GM.
- Cephalalgia. 2023 Jun;43(6):3331024231180564. doi: 10.1177/03331024231180564.

Clinical Tools and Scales in Practice



- Clinical scales to assess depression, catastrophizing, and other factors in daily practice
- These tools help predict treatment responses and guide therapy selection
- For example, allodynia is used to educate patients on the timing of acute treatments, as triptans (work on first order neurons) are less effective once allodynia occurs (2^{nd} -3^{rd} order neurons, driving neuronal sensitization)

Blood Markers for Early Treatment Prediction



- Measuring CGRP levels in blood samples early in treatment can help predict patient response
- A significant decline in CGRP levels within the first few weeks of treatment correlates with better outcomes, enabling more personalized and cost-effective care
- Still not available in clinical practice, not yet validated, there is significant variability

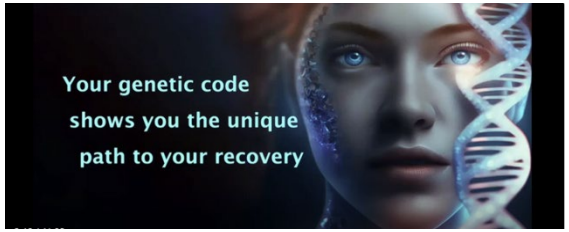
de Vries Lentsch S, Garrelds IM, Danser AHJ, Terwindt GM, MaassenVanDenBrink A.
J Headache Pain. 2022 Sep 12;23(1):120. doi: 10.1186/s10194-022-01483-z.
PMCID: PMC9464612

Summary of Biomarkers and Predictability

- Depressive symptoms (clinical marker): patients reporting depressive symptoms were less likely to respond to monoclonal antibody treatments in the Leiden group's studies
- Allodynia (clinical marker): presented as a negative predictor of treatment response (including for monoclonal antibodies), and also linked to worse likelihood of reverting from chronic to episodic migraine
- Early change in blood CGRP (biologic marker): a decline in CGRP measured after ~2–4 weeks of starting treatment was described as promising—the greater the decline, the more likely patients were to be responders months later (an "early prediction" signal).

Genetic research maps migraine vulnerability across four biological systems

- Brain chemistry (neuronal communication via neurotransmitters)
- Inflammation (immune signaling)
- Energy production (high energy demands of brain tissue; migraine linked with impaired energy availability)
- Vascular system (blood flow–related issues; small white matter spots as tied to vascular problems)

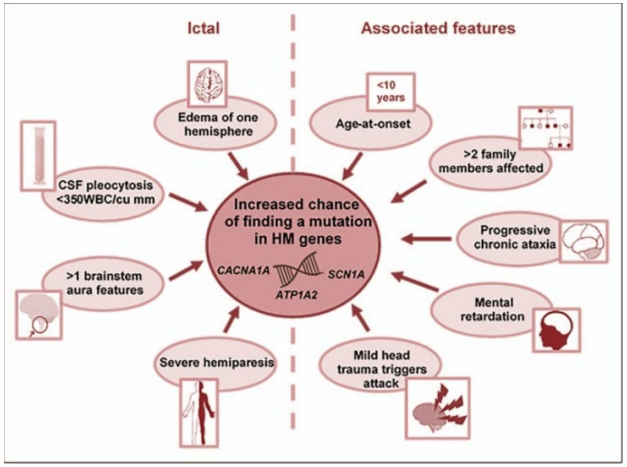


Genetics

- Useful in rare cases
  - Hemiplegic migraine
  - Not helpful in typical migraine

Hemiplegic Migraine

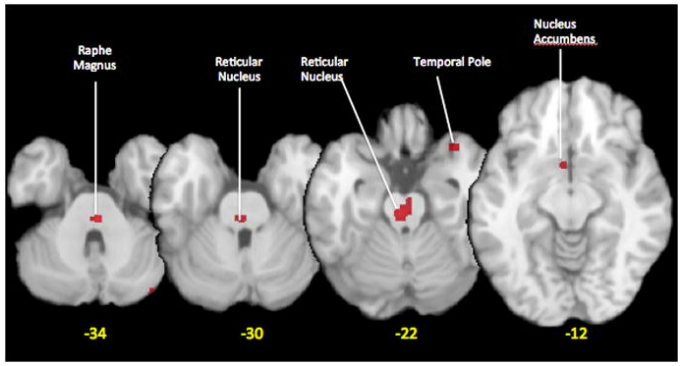
- Migraine with aura in which the aura phase includes transient motor weakness.
- CACNA1A, ATP1A2, and SCN1A have been identified
- Mutations in these three genes predict increased neurotransmitter and potassium ion levels at the synaptic cleft, which facilitates cortical spreading depolarization, the phenomenon underlying the migraine aura

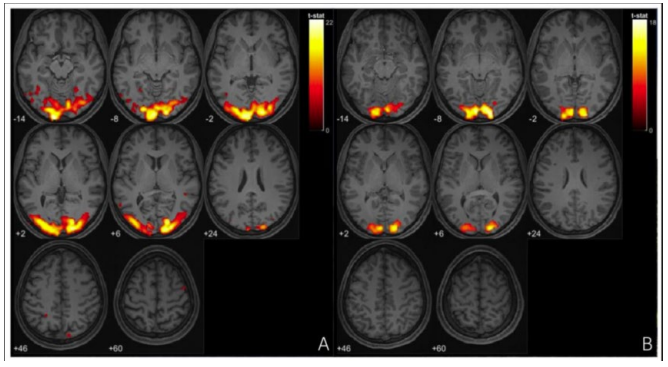


Review Handb Clin Neurol. 2024:199:353-365. doi: 10.1016/B978-0-12-823357-3.00015-X. Irene de Boer 1, Jakob M Hansen 2, Gisela M Terwindt 3
PMID: 38307656 DOI: 10.1016/B978-0-12-823357-3.00015-X

Neuroimaging

- Brainstem/hypothalamic activation
- High resolution 7T MRS is able to show changes in the glutamatergic system towards a triggered migraine attack, by revealing an increased GABA concentration associated with the onset of a migraine attack.
- It is still a research tool





Onderwater GLJ, Wijnen JP, Najac C, van Dongen RM, Ronen I, Webb A, Zielman R, van Zwet EW, Ferrari MD, Kan HE, Kruit MC, Terwindt GM. Neuroimage Clin. 2021;32:102889. doi: 10.1016/j.nicl.2021.102889. Epub 2021 Nov 24. PMID: 34911195

Wearables and Future Directions

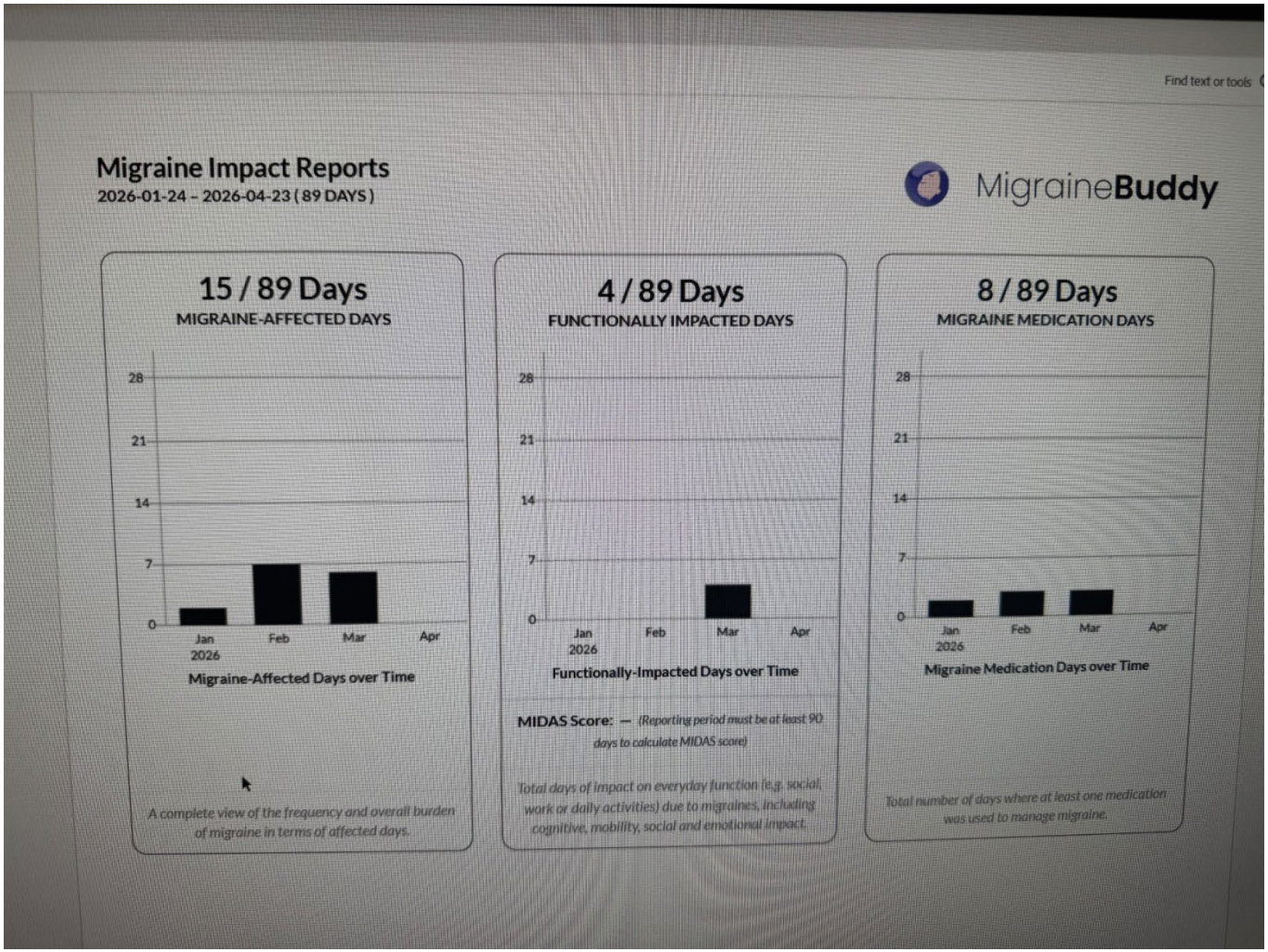
- Wearable devices, such as a VEP-EEG cap, are utilized by patients to predict migraine attacks
- These devices, combined with data from smartphones and other wearables, aim to provide real-time insights into upcoming attacks
- Promising area for future research

Petrušić I. Cephalalgia. 2025 Jul;45(7):3331024251363568. doi: 10.1177/03331024251363568. Epub 2025 Jul 30

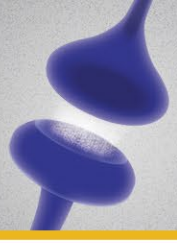
Danelakis A, Stubberud A, Tronvik E, Matharu M. Life (Basel). 2025 Jun 4;15(6):909

Stubberud A, et al. Cephalalgia. 2023 May;43(5):3331024231169244. doi: 10.1177/03331024231169244.

Migraine Buddy



American Headache Society: Updated Guidelines

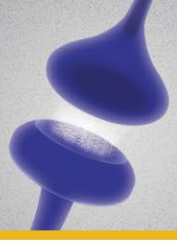


- Treating early, and framing care as potentially disease-modifying rather than only attack-aborting
  - Late and incomplete treatment leads to increased headache frequency, risk to evolve to chronic state
- CGRP therapies position and OnabotulinumA as first-line considerations for prevention.
- ED-care guidance discouraging opioids; endorsing dopaminergic antagonist approaches; and noting that peripheral nerve blocks are recommended as a first-line ED option, with prochlorperazine upgraded to level A
- Typical protocol in our region: prochlorperazine 10 mg, Diphenhydramine 12.5 or 25 mg, Magnesium 1 gm plus minus Ketorolac 15 or 30 mg

What “matters” to patients..

- Expanding migraine-free intervals
- Interictal improvements such as mood/sleep in some CGRP data. Decreased fear of potential attacks
- Metabolic effects, e.g., atogepant-associated potential for weight loss

More options for the young

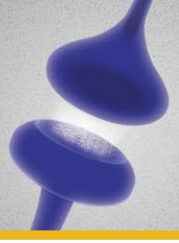


- Pediatric prevention
- The SPACE trial is referenced as showing preventive efficacy of fremanezumab in ages 6–17 with episodic migraine
- Acute and Chronic migraine pediatric studies are noted as ongoing.

Better tolerated Antihypertensive drugs

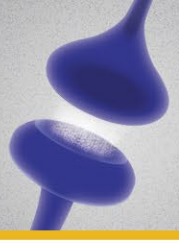
- A candesartan placebo-controlled study is mentioned as supporting efficacy at 16 mg dose daily
- I often start at a lower dosing (e.g., 8 mg) in some patients

Evidence Supporting CGRP Therapies



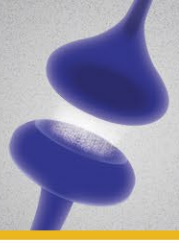
- New trials report responder rates (50%, 75%, or 100% reduction in migraines), a unique metric not seen in older therapies
- CGRP therapies are effective even in patients who have failed multiple other preventive treatments or those with medication overuse headaches

Costs vs Patient Impact



- CGRP therapies are more expensive than older nonspecific treatments, but they are specifically designed for migraines and offer significant benefits.
- Beyond medication costs, these therapies reduce the broader costs of migraines, including impacts on patients' families, employers, and overall quality of life (indirect cost)
- Patients report life-changing improvements, including better function and well-being between migraine attacks

Tailoring Preventive Treatments

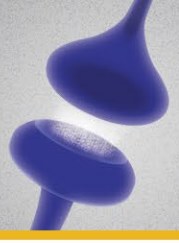


- Preventive treatment is typically recommended for patients with 4 or more headache days per month, or 2 or more disabling monthly attacks
- Older nonspecific therapies are often chosen based on comorbidities (e.g., beta-blockers for hypertension, tricyclic antidepressants for insomnia, depression)
- However, these older treatments have significant tolerability issues, leading to poor adherence (only 17% remain on them after a year).
- CGRP therapies show higher adherence due to better tolerability and effectiveness, making them a strong first-line option for both episodic and chronic migraines

Rational Combination Therapy: When and How

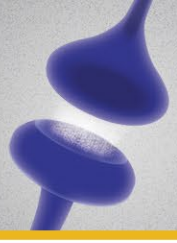
- When a single approach doesn't get a patient close to "migraine freedom." The patient is better but not well, room for improvement and an ambitious goal of migraine freedom
- Initiate/consider adding a second preventive when a patient improves but remains meaningfully symptomatic (e.g., chronic migraine 24 headache days/month → 12 days/month on one preventive); 12 days/month is "not good enough" another therapy is added to further decrease the frequency
- Practical trigger: when the patient still needs prn medication (acute) treatment frequently, indicating incomplete control despite preventive therapy

Rational Combination in the acute setting



- If an acute option works only “most of the time” (example given: ~80% response)—because 1 in 5 attacks still leaves the patient not functioning within ~2 hours—consider switching classes or combining acute treatments
- Triptans have different pharmacokinetics, we can tailor the triptan and route of administration to the attack characteristics

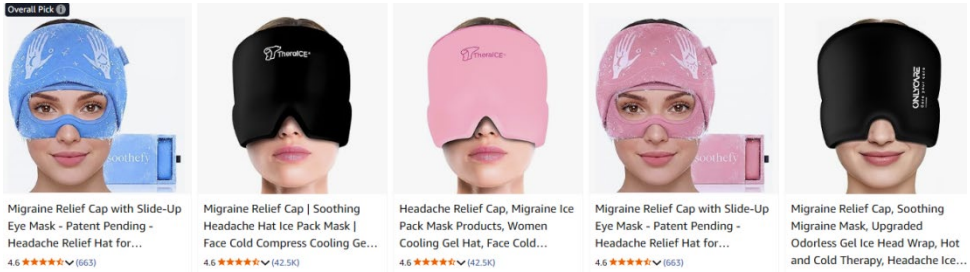
Rational combinations



- Examples of “rational” combinations mentioned: adding an anti-CGRP monoclonal antibody or a gepant to onabotulinumtoxinA (Botox) for prevention
- For acute care, using triptan + anti-inflammatory (including an FDA-approved combo tablets, like Treximet or Symbravo)
- Or layering an anti-inflammatory/triptan with a gepant
- Add adjuvant medications like antiemetics (prochlorperazine, promethazine, chlorpromazine) or antihistaminics (Diphenhydramine) in the evenings for rescue
- Add a muscle relaxant if significant cervical muscle spasm

Integrating temperature therapy into your migraine toolbox

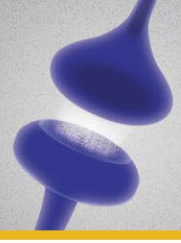
- Ice/heat are positioned as adjunctive tools alongside medications and other supports (e.g., adjuvant medicaitons, relaxation strategies).
- Emphasis is placed on building self-efficacy by having multiple options and testing combinations (medication + ice/heat ± behavioral approaches) to identify an individual "best strategy"
- The chosen combination should be implemented early at attack onset to give the best chance of recovery



GLP1-RA in IIH

- Potentially disease-modifying by lowering intracranial pressure (ICP) via both direct CSF effects and weight-related mechanisms
- Direct ICP mechanism: GLP-1 RAs have been shown to lower intracranial pressure by decreasing CSF secretion at the choroid plexus
- Weight-related mechanism: They also promote weight loss, which may improve IIH by reducing the obesity-related "resistance" to CSF drainage
- Clinical signal (trial + real-world): The speaker cites randomized clinical trial data showing rapid and sustained ICP reduction (reported as early as 2.5 hours, then 24 hours, and out to 12 weeks) in women with IIH, with no serious safety signals mentioned

Clinical Outcomes beyond Weight Loss

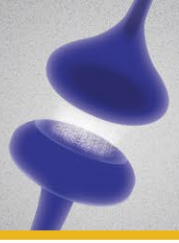


- Propensity cohort data (~6,000 IIH patients)
- Showing lower acetazolamide requirements
- Reduced headache frequency
- Decreased need for shunt insertion in GLP-1 users—effects appear relatively independent of weight loss

The Gut Matters in Migraine

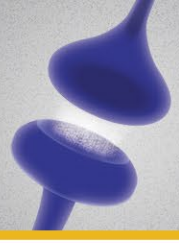
- Migraine as a systemic, brain-centered disorder with meaningful gut and immune contributions, not just a headache syndrome
- High population burden and disability impact, motivating more complete mechanistic models that include the microbiome
- GI symptoms and comorbid gut disorders are potentially central to disease expression and treatment response, rather than incidental

Microbiome–gut–brain axis: bidirectional pathways relevant to migraine



- "Top-down" CNS effects on gut function via the autonomic nervous system and migraine-relevant neuropeptides (e.g., CGRP, substance P, VIP), can also shape microbial composition
- "Bottom-up" gut microbial outputs (neurotransmitters/metabolites such as GABA, serotonin precursors, short-chain fatty acids, inflammatory mediators) that influence barrier integrity, neuroinflammation, pain thresholds, mood/anxiety, and migraine susceptibility
- The vagus nerve is a key conduit. FDA-approved noninvasive vagal nerve stimulation as proof-of-concept that modulating this pathway can treat migraine

GI symptoms during attacks and impact on acute treatment

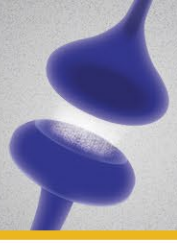


- GI symptoms are common and clinically meaningful: ~75% of attacks involve nausea; ~⅓ involve vomiting; many also report early satiety, bloating, constipation/diarrhea, reflux
- Nausea/vomiting to brainstem pathways adjacent to the trigeminovascular system (including the nucleus tractus solitarius/“vomiting center”), involving serotonin, CGRP, and substance P signaling
- Prominent nausea/vomiting reduces reliability of oral medication absorption, creating a cycle of uncontrolled pain and escalating symptoms

Key mediators at the gut–migraine interface

- **Serotonin**: most serotonin is produced in the GI tract and influenced by microbial metabolites; disruption may alter both central pain processing and peripheral motility/secretion
- **CGRP**: rises during attacks; also has gut roles (antimicrobial activity, appetite suppression, reduced gastric acid secretion). CGRP-targeting therapies can have GI effects (e.g., constipation), consistent with extra-CNS CGRP physiology
- **GABA**: gut bacteria may synthesize/modulate GABA signaling; preclinical work suggests depletion of GABA-producing bacteria lowers pain thresholds and restoration may reverse hypersensitivity

Common gut disorders associated with migraine and migraine-variant GI phenotypes

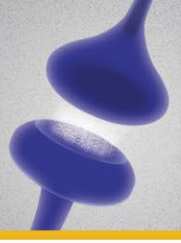


- IBS
- Celiac Disease
- H. Pilori
- Functional Dyspepsia
- Abdominal Migraine and Cyclic Vomiting

Integrate pharmacology with gut-targeted lifestyle strategies

- **Diet:**
  - low-glycemic patterns, higher fiber intake to support SCFA producers, omega-3s to reduce systemic inflammation, reducing ultra-processed foods (emulsifiers/additives), and individualized trigger elimination; notes Mediterranean-style eating as a practical framework with emerging migraine data

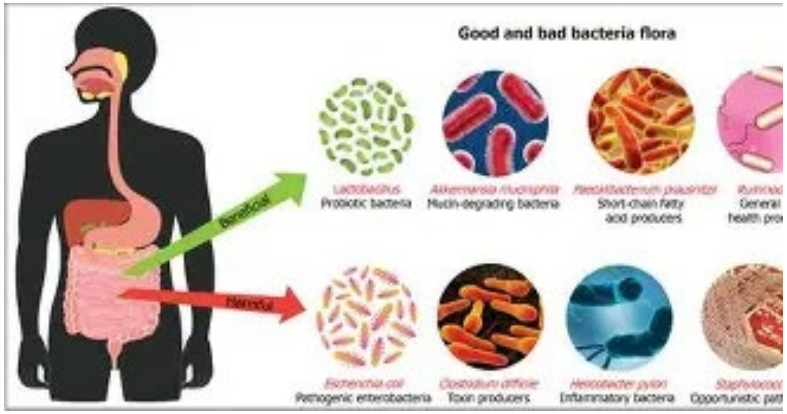
Integrate pharmacology with gut-targeted lifestyle strategies



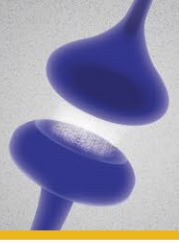
- Prebiotics/synbiotics
  - prebiotics are like a “fertilizer” for beneficial microbes; slow introduction to reduce GI intolerance
  - synbiotics combine pre- and probiotics to support colonization/function

Integrate pharmacology with gut-targeted lifestyle strategies: supportive tools

- Stress, sleep, and exercise
  - chronic stress and sleep disruption is related to barrier dysfunction, dysbiosis, and lower pain thresholds
  - mindfulness, diaphragmatic breathing, regular moderate exercise, biofeedback, CBT
  - consistent sleep habits



Integrate pharmacology with gut-targeted lifestyle strategies

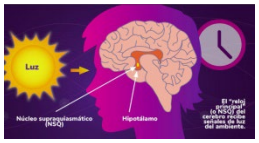


- Acute care delivery
  - matching route of acute therapy to GI status
  - use antiemetics when indicated
  - consider non-oral routes (nasal, subcutaneous, IV, device-based neuromodulation, suppositories in select cases) when nausea/vomiting/gastroparesis limit oral absorption

Emerging targets

- Several mechanistic directions (e.g., potassium/ATP channels) TRPM3 as a first-in-class target with phase 2 data anticipated, including interest in sex differences in vasoactive responses
- PACAP pathway as an important emerging area with multiple monoclonal antibodies in development; the HOPE phase 2 trial is referenced as showing reduced monthly migraine days, with follow-up efficacy but some negative studies in the pathway
- Targeting the PACAP ligand may be more effective than targeting the PACAP-1 receptor, based on synthesis of evolving results

- Circadian/sleep genes



- Adrenergic stress-response genes
- Dopamine (for some)
- GABA/glutamate (for most)
- BDNF (neuroplasticity)
- Neurotransmitter breakdown enzymes
- **“Es complicado”**

Thank you for your attention

- Happy Mother's day