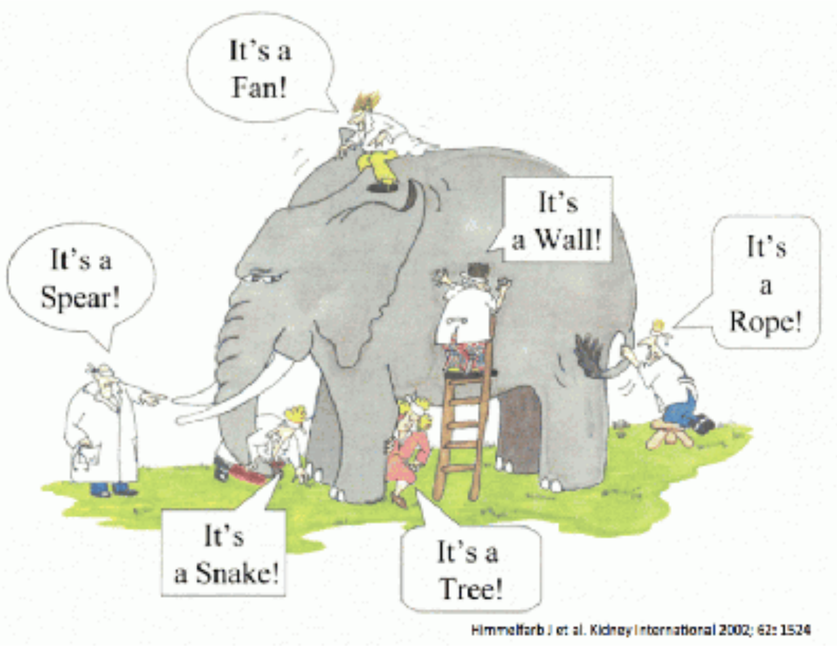
Update on H(EDS)/HSD, PoTS and MCAS in relation to headache

Dr Kate Barnes BASH GP Meeting
24th October 2025

Do you have a ‘difficult’ patient?

- Chronic fatigue
- Fibromyalgia
- Post Covid Headache
- Polysymptomatic: IBS, Endometriosis, IC
- Concomitant Auto-immune disease
- Poor response to tried treatments
- Drug sensitivities



Himmelfarb J et al. Kidney International 2002; 62: 1524

Go back to history:

These patients have a very clear memorable start to their ill-health/headache

ASK:

WHEN did you become ill/when did headache start?

WHAT happened?

Infection (eg EBV, Covid, Lyme)

Head injury/whiplash

Vaccine (eg Covid)

Emotional Stress eg bereavement

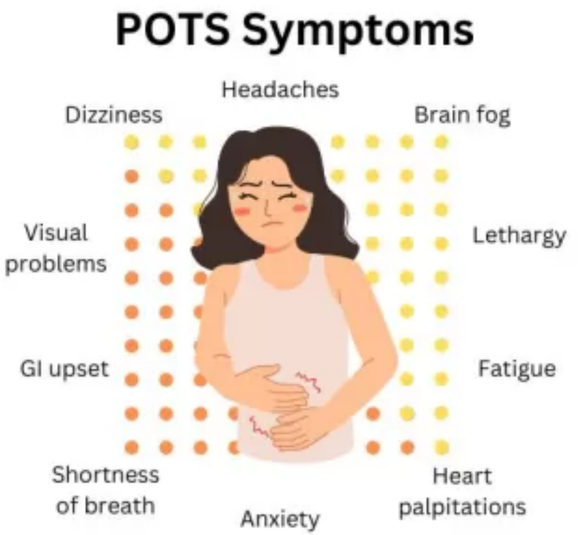
ALARM BELL; Headache is a symptom/part of overarching illness likely to be affecting connective tissue, autonomic nervous system, immune system ie the Tri-fecta (H(EDS)/PoTS/MCAS)

History and Exam for Hyper-mobility

- Do you injure yourself easily (sprains, subluxations, dislocations)
- Do you bruise easily?
- Were you able to contort your body/do weird party tricks as a child?

- BEIGHTON SCORE:
- In headache clinic look for shoulder hyper-mobility (prayer sign) - soft marker for CCI
- If time/interest fill in 2017 Diagnostic Checklist for H(EDS)/HSD https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf

Looking for PoTS (Dysautonomia)



Active Stand Test Protocol:

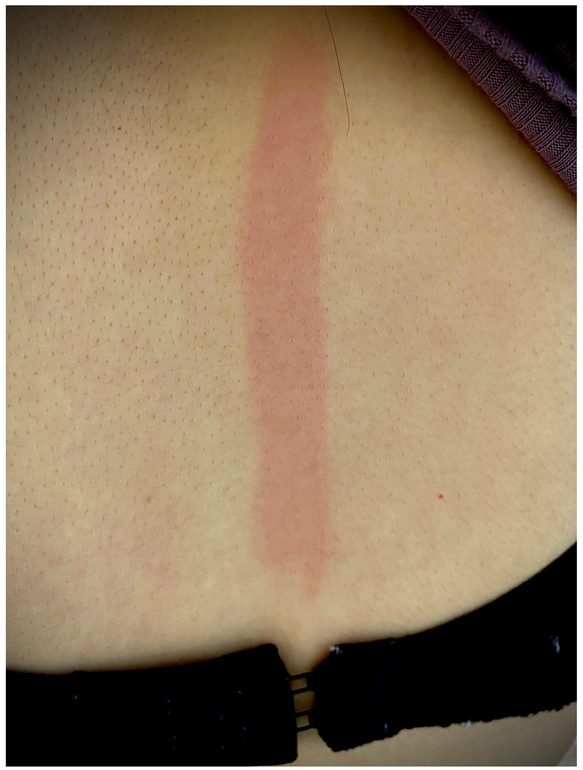
- Please get an electronic arm cuff BP monitor
- Have this ready on your bed-side table the night before
- On waking check both pulse and BP and record
- Stand up beside bed for at least 3 minutes (or as long as you safely can), max 10 minutes and check pulse and BP again and record
- Please do this for a week (7 times) and send readings of both pulse and BP

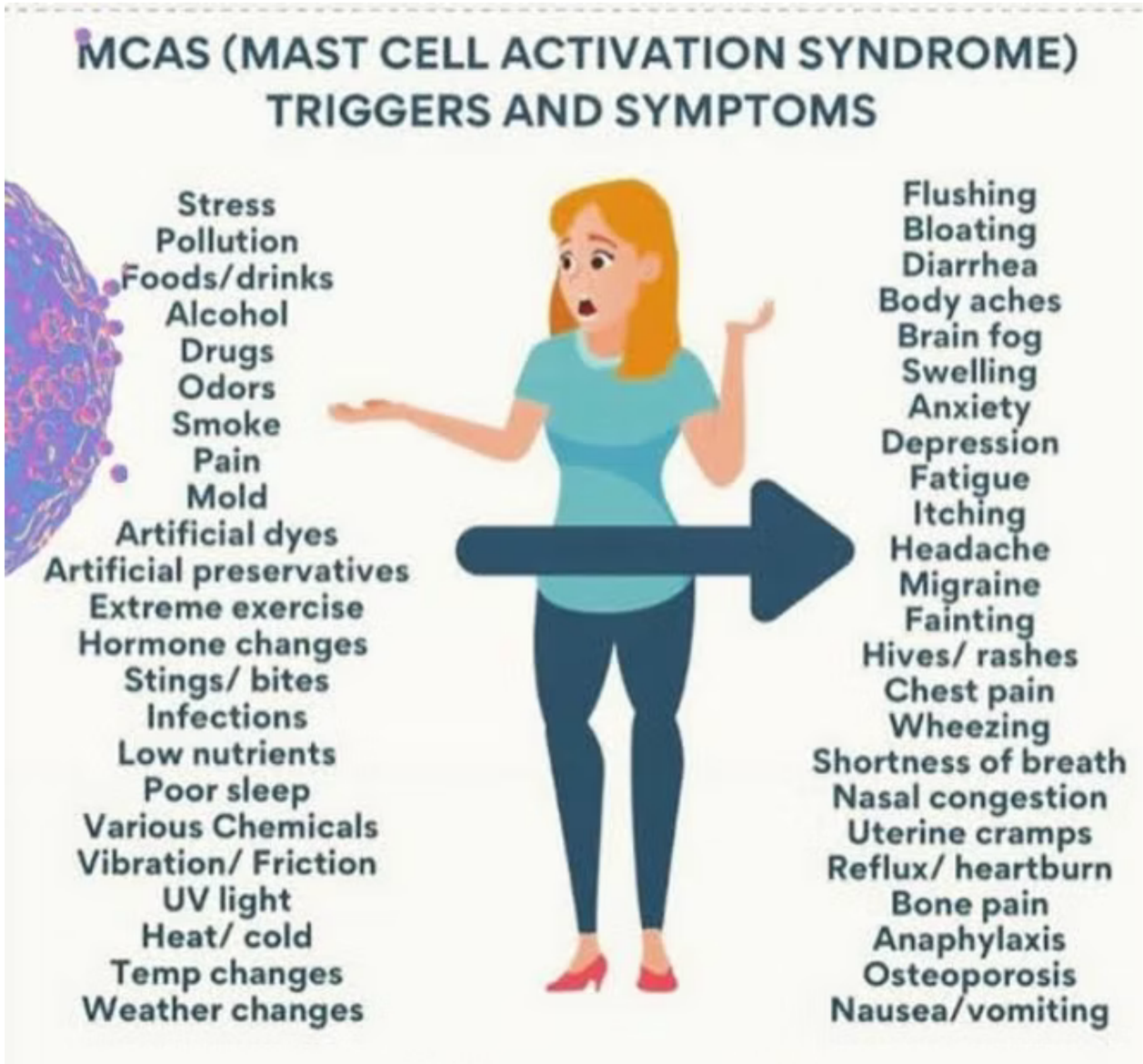
A rise in heart rate greater than 30 beats per min from lying to standing

BP important to differentiate normal (BP low/stable) from hyper-adrenergic PoTS (BP rises) and OH

MCAS symptom and trigger checklist:

Ask them to fill in questionnaire:
Examine for dermatographia:





Why does making these diagnoses matter?

- Further consideration of cause(s) of headache for targeted treatment: may need to include consideration of CCI, CSF leak, in addition to PoTS and MCAS
- Treatment choices may need to include multiple medication (including supplements) to manage different causes contributing to headache
- Consider priorities in treatment and treat with one medication initially, start low and build up
- These patients are generally hyper-sensitive to medication
- Treating PoTS will improve MCAS
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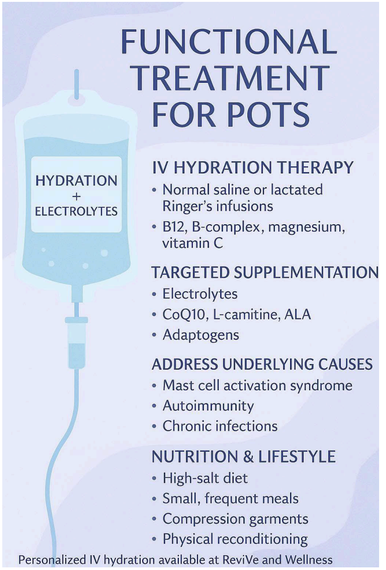
- Some treatments for migraine/headache can make these patients worse eg B Blockers (increase fatigue, lower BP), Candesartan (need ACE affect MCA via KKS) so need to be avoided
- Amitritpyline/dosulepin can be useful as they are mast cell stabilisers

Treatment of PoTS

Compression (to abdomen eg ‘skins’ leggings)

Increase fluid AND salt intake (electrolyte solutions)

Future: iv hydration

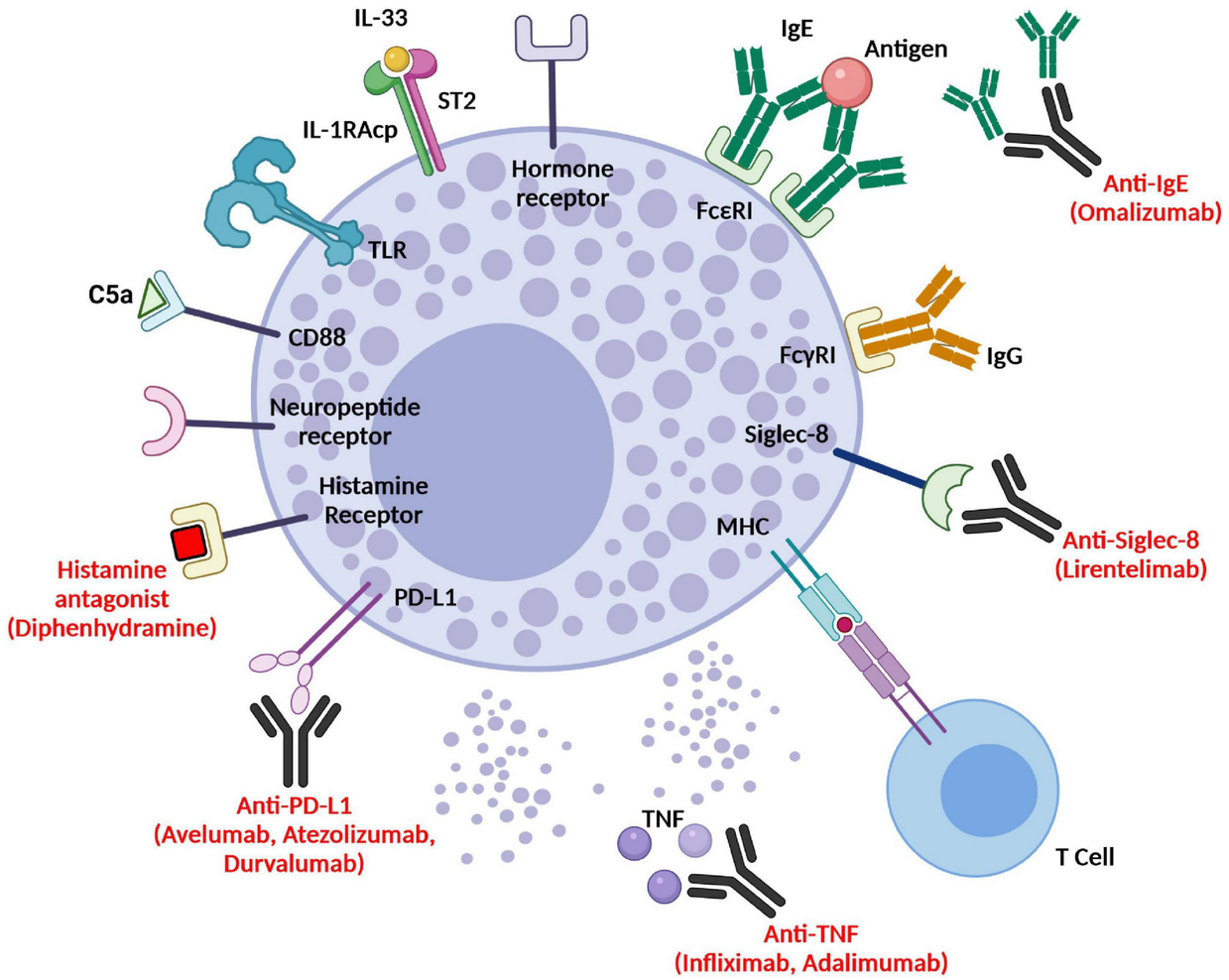


Medication:

- pyridostigmine (cholinesterase inhibitor - shown to be useful in Long Covid - dysfunction of AchR)
- midodrine (alpha-agonist - cause vasoconstriction, increases BP)
- ivabradine (slows down heart rate by acting on SA node - doesn’t lower BP)
- Future: IVIG, plasmapheresis

Treatment of MCAS:

Common Mast Cell Activation Mechanisms, Responses, and Therapeutic Targets



Activators

Complement (C5a)
PAMPs
Fc Receptors (IgE & IgG)
Neuropeptides
Hormones
Serine Proteases
Cytokines (IL-33)

Responses

Rheumatoid Arthritis
IL-8, TNF, IL-10

Multiple Sclerosis
IL-17, tryptase, chymase

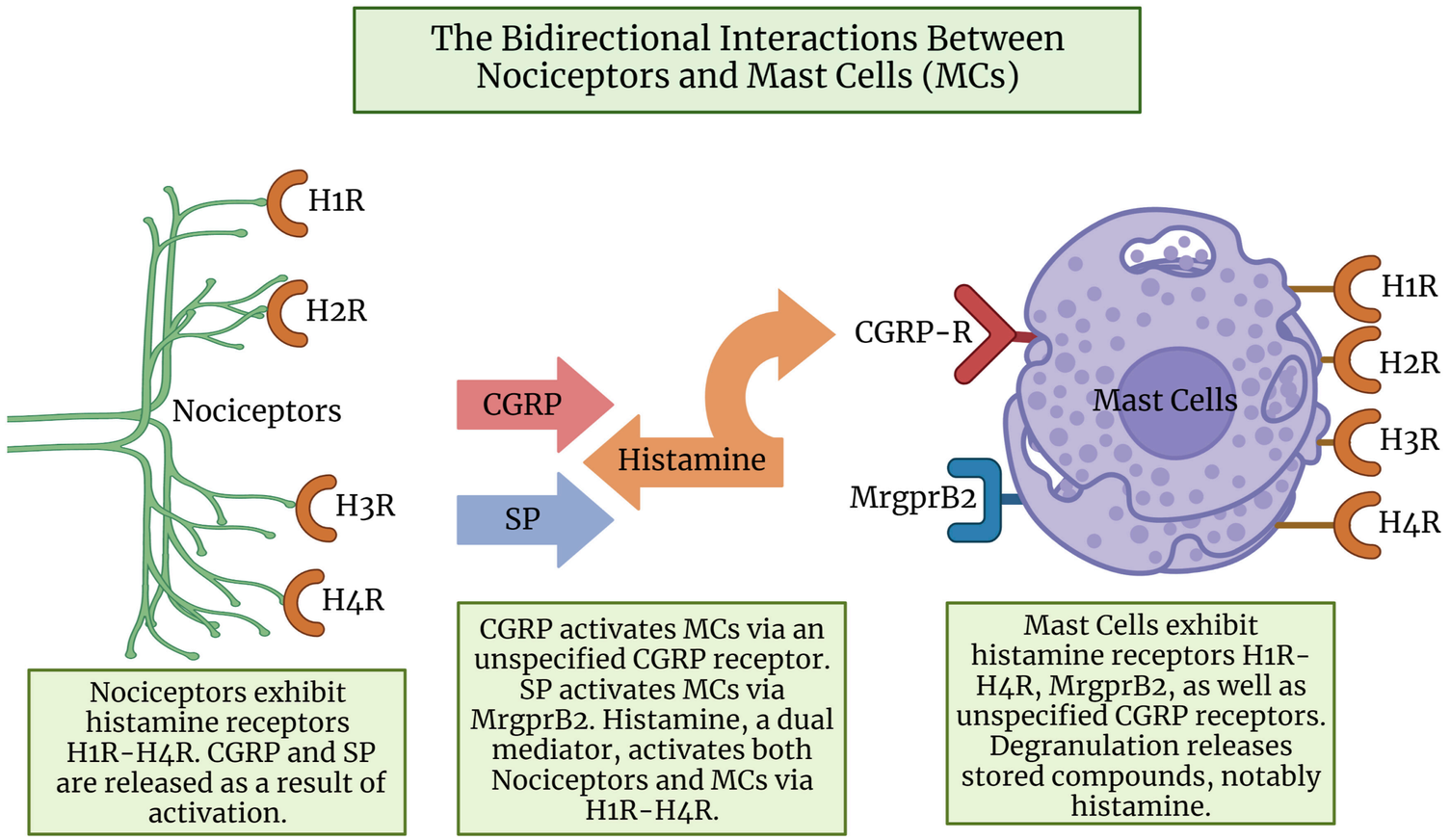
Type 1 Diabetes
IL-6

Inflammatory Bowel Disease
TNF, histamine

Therapeutics

Anti-IgE
Anti-Siglec-8
Anti-TNF
Anti-PD-L1/PD-L2
Histamine antagonists

Bi-directional interactions between sensory neurons and mast cells



Treating MCAS with reference to headache

Histamine:

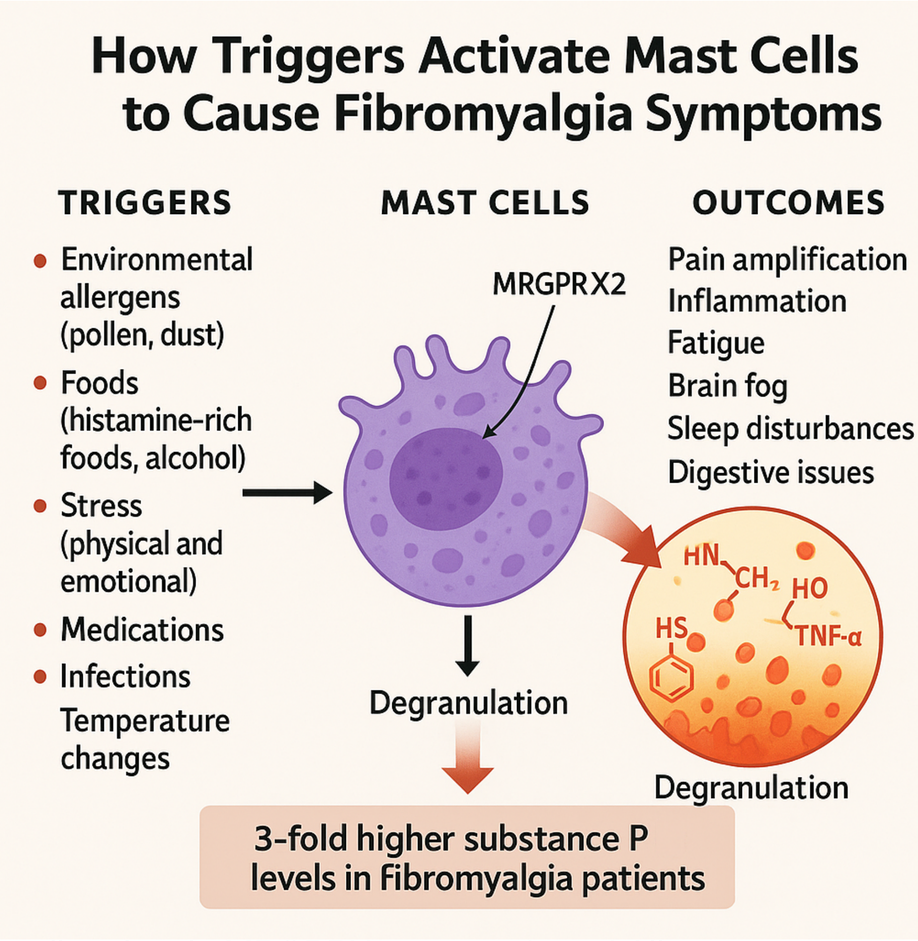
- Start with **H1 blocker** (eg fexofenadine) Start low and increase often to 180 mgs bd or tds
- Add in **H2 blocker** famotidine (eg 20 mg od, increasing to 40 mg bd) Useful if additional gut issues, endometriosis NB contains lactose
- Consider a **mast cell stabiliser** eg ketotifen. Start 0.5 mg, increase to 1 mg bd or 2 mg nocte (can help sleep) NB contains lactose
- Other mast cell stabilisers: Amitriptyline/dosulepin, Quercetin, Vit D (with K2), Vit C
- NB Check **DAO Common cause of histamine intolerance in gut and contributes to headache.** Can buy DAO supplements OTC

Low Dose Naltrexone (LDN)

- At low doses has an antagonist effect on Toll-like receptors (TLR) including TLR4
- There are TL4 receptors on both microglial (phagocytes) and mast cells.
- Mast cells directly effect microglial cells via activation cascades (pro-inflammatory cytokines (TNF, TGF-B, il-1B, IFN-gamma, Substance P, NO)
- LDN therefore reduces pro-inflammatory cascades
- Tricks the body into producing endogenous opioid by briefly binding to receptors
- Observational studies show benefit in Long Covid
- Use 1/10th dose used in opioid addiction
- Good service offered by Dickson's Pharmacy Glasgow
- ci in those on opioid analgesics
- Liquid dose titrated slowly up to maximum dose of 4.5 mg/day (should be stopped 7 days before surgery) Start at 1-1.5 mg a day, increased by 1 mg every week. Short half-life (4-6 hrs) but boosts endogenous opioid for 18-24 hours Side -effects - short-lived insomnia/vivid dreams.
- Can take 8-10 weeks for max response.

Important Mechanism for MCA in FM/Migraine

- The MRGPRX2 receptor plays a role in recognising pathogen associated molecular patterns (PAMPS)
- MRGPRX2 receptors (G protein coupled receptors) mediated via IgG (found particularly in those with connective tissue pain (fibromyalgia)
- Also skin (atopic dermatitis, chronic urticaria, allergic contact dermatitis)) and oral mucosa
- Unlike most G protein coupled receptors receptor is activated by diverse array of molecules including Substance P and also by neuropepetide PA-CAP-38 from nearby sensory neurons
- Also activated by cationic drugs eg fluroquionolone (ciprofloxacin), opioids (codeine, Opioids (morphine), contrast media causing pruritus, vasodilation and hypotension
- Activated by Neuro-muscular blocking agents used in GA eg atracurium, rocuronium muscular blockers
- Responsible for skin reactions at injection sites, chronic inflammatory conditions, biofilms, non-histaminergic itch and probably food intolerances
- Inhibitors of MRGPRX2 could prevent mast cell degranulation and be used to treat FM,migraine, post op pain, allergic reaction Wollam J, Solomon et al Inhibition of mast cell degranulation by novel small molecule MRGPRX2 antagonists. J Allergy Clin Immunol. 2024 Oct;154(4):1033-1043. doi: 10.1016/j.jaci.2024.07.002. Epub 2024 Jul 5. PMID: 38971540.



H(EDS)/HSD Update (Scientific Symposium Toronto Sept 2025)

- HEDGE Study (EDS Society) - looking for a common gene in H(EDS) - no common gene - therefore her multiple variants

- NOW recognised that h(EDS)/HSD are part of the same condition. In fact - those with HSD (less hypermobility) may have more co-morbidities eg other auto-immune disease, than those diagnosed with h(EDS)

- Widely recognised that although 20% population are hyper-mobile, it's the way genes are expressed (epigenetic) within environment (hormonal, autonomic, immune) that is significant in causing vulnerability. Generally a known trigger/insult creates a perfect storm ('last straw that broke the camel's back')

- Diagnostic Odyssey Study: Years +++ to diagnosis (greater than any other rare disease), clinician-associated trauma, misdiagnosed with either mental health disorder or ME/CFS

https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63857 Bridging the Diagnostic Gap for Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders: Evidence of a Common Extracellular Matrix Fragmentation Pattern in Patient Plasma as a Potential Biomarker

American Journal Clinical Genetics Sept 2024

Currently, the 2017 diagnostic criteria for hEDS are used, with non-qualifying cases classified as HSD, although the distinction remains debated.
We previously showed extracellular matrix (ECM) disorganization in both hEDS and HSD dermal fibroblasts involving fibronectin (FN), type I collagen (COLLI), and tenascin (TN), with matrix metalloproteinase-generated fragments in conditioned media.

Here, we investigated these fragments in patient plasma using Western blotting across diverse cohorts, including patients with hEDS, HSD, classical EDS (cEDS), vascular EDS (vEDS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and osteoarthritis (OA), and healthy donors, uncovering distinctive patterns.
Notably, hEDS/HSD displayed a shared FN and COLLI fragment signature, supporting their classification as a single disorder and prompting reconsideration of the hEDS criteria.
Our results hold the promise for the first blood test for diagnosing hEDS/HSD, present insights into the pathomechanisms, and open the door for therapeutic trials focused on restoring ECM homeostasis using an objective marker. Additionally, our findings offer potential biomarkers also for OA, RA, and PsA, advancing diagnostic and therapeutic strategies in these prevalent joint diseases

Maria Colombi: Found fibronectin products in the blood, disappeared when gave doxycycline to rats in vivo - mode of action likely to be doxycycline’s effect on MMPs which are building blocks for ECM in connective tissue

Griggs M, Daylor V, Petrucci T, Weintraub A, Huff M, Willey S, Byerly K, Loizzi B, Morningstar J, Ball LE, Bethard JR, Drake R, Sharma A, Eichinger JK, Nichols M, Kautz S, Shapiro S, Maitland A, Patel S, Norris RA, Gensemer C.
Proteomic discoveries in hypermobile Ehlers-Danlos syndrome reveal insights into disease pathophysiology. Immunohorizons. 2025 Sep 17;9(10):vlaf044. doi: 10.1093/immhor/vlaf044. PMID: 40972649; PMCID: PMC12448790.

Proteomic analysis revealed 35 differentially expressed proteins in hEDS, with 43% involved in the complement cascade and 80% linked to immune, coagulation, or inflammatory pathways. Our findings indicate a systemic immune dysregulation, particularly involving the complement system and profibrotic cytokines, as a common feature in hEDS pathophysiology.

These findings challenge the traditional view of hEDS as solely a connective tissue disorder and support a revised paradigm that includes innate immune dysfunction.

Conclusions:

- These conditions are likely to have their origin in immune dysfunction.
- There are treatments and life style advice that can be extremely helpful with an approach that is holistic and integrated
- Interested GPERs are well-placed to manage these complex patients
- There are reasons to be optimistic with further developments in research especially since Covid