MCAS and Pain

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MAST CELL ACTIVATION SYNDROME

A condition in which the mast cells of the body release excessive amounts of inflammatory chemicals in response to triggers.

The release of these chemicals causes a variety of allergy-like symptoms, even though you may or may not have a testable allergy.

Normal number of mast cells, but they are more reactive than normal.
Mast cells are present in many tissues, activation can cause a very wide range of symptoms.
From only a few symptoms and be very functional, or many symptoms and very disabled.

Symptoms can also be acute, including anaphylaxis, or they may be chronic. Individuals can have any combination of these issues, and it can change at any time.

Similar in symptoms to Systemic Mastocytosis (SM), but in SM there are an excessive number of mast cells produced in the body.

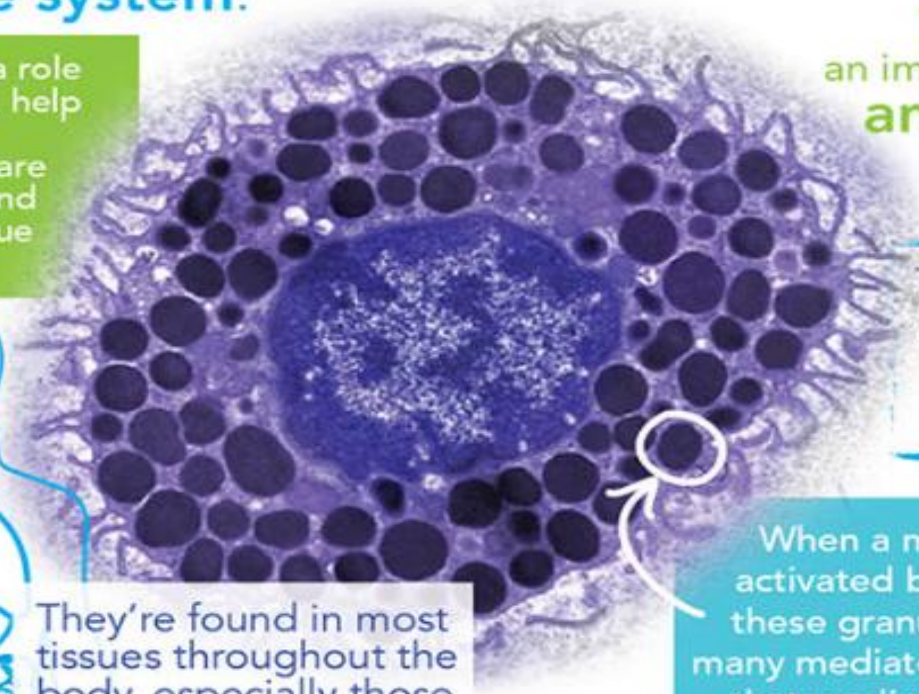
What is a MAST CELL?

Mast cells are a part of the **immune system**.

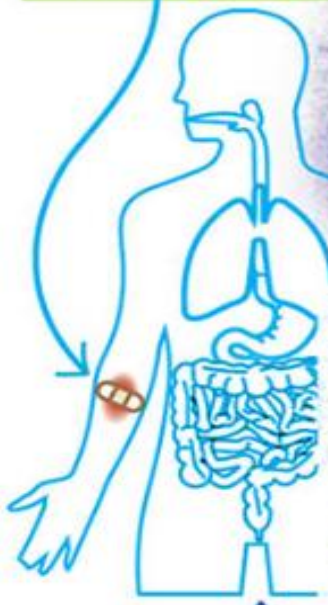
Mast cells are well-known for releasing histamine during allergic reactions, such as in pollen or insect sting allergies.

They play an important role in **anaphylaxis!**

Mast cells play a role in inflammation, help defend against pathogens and are involved in wound healing and tissue repair.



They can detect and respond to foreign substances.



They're found in most tissues throughout the body, especially those that interact with the outside environment, including the lungs, gastrointestinal tract and skin.

When a mast cell is activated by a trigger, these granules release many mediators (chemicals that mediate reactions leading to symptoms).

histamine is a mediator

MAST CELL DISEASE happens when these cells aren't behaving normally.

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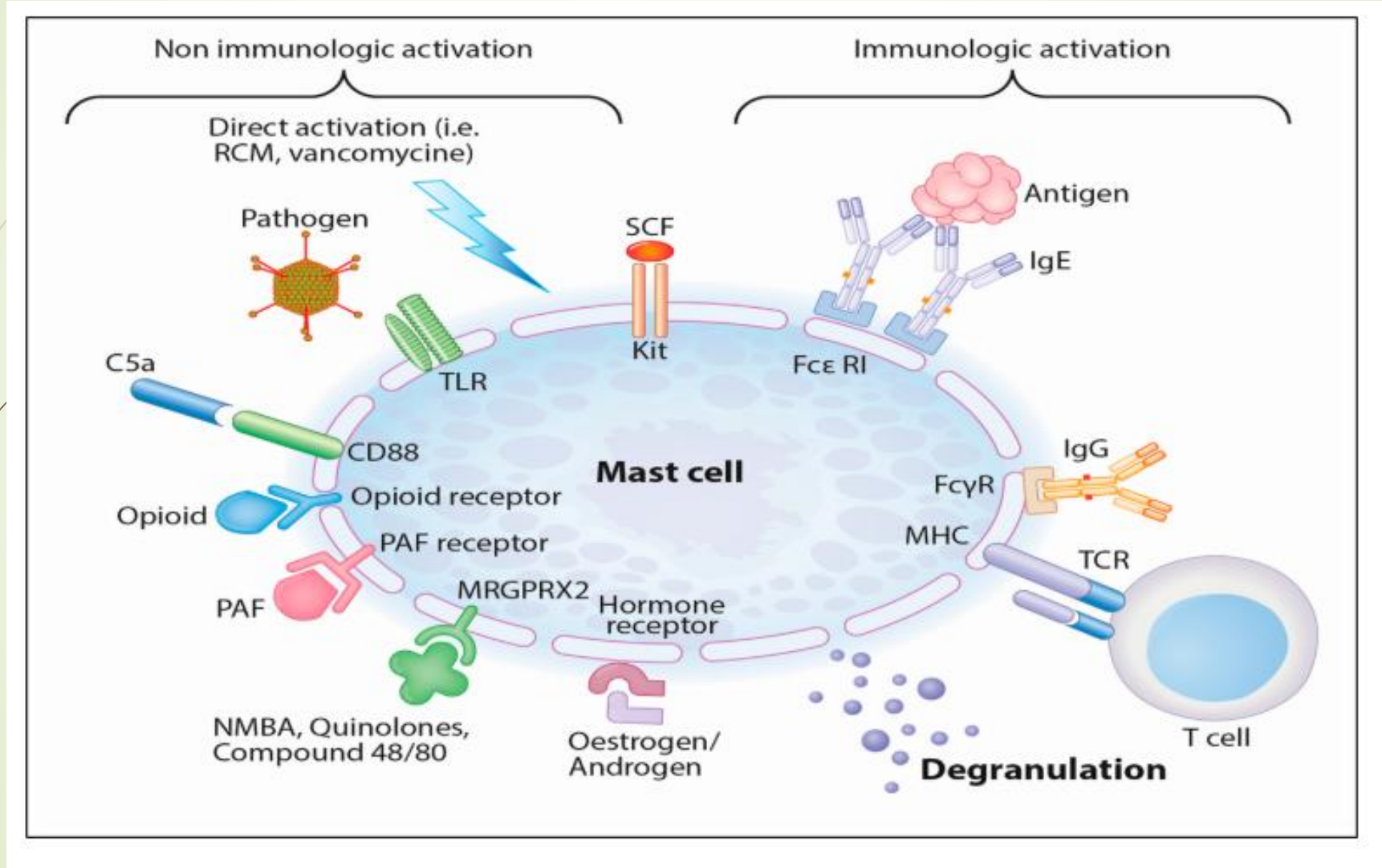

Non immunologic activation
Immunologic activation
Direct activation (i.e. RCM, vancomycine)
Pathogen
SCF
Antigen
IgE
Kit
TLR
Fcε RI
C5a
CD88
Mast cell
IgG
FcγR
Opioid receptor
Opioid
MHC
PAF receptor
TCR
PAF
MRGPRX2
Hormone receptor
T cell
NMBA, Quinolones, Compound 48/80
Oestrogen/ Androgen
Degranulation

WHAT IS INFLAMMATION?

Natural immune response to injury, infection, or harmful irritants.

It is a vital defense mechanism.

White blood cells, antibodies, and fluid are sent to the affected area to fight off pathogens, clear out damaged cells, and begin the healing process

Good Inflammation (Acute)

Short-term response to injury or sickness= ‘fire alarm’.

The body sends extra blood and cells to fix a cut or fight a cold. Stops germs and heals tissue.

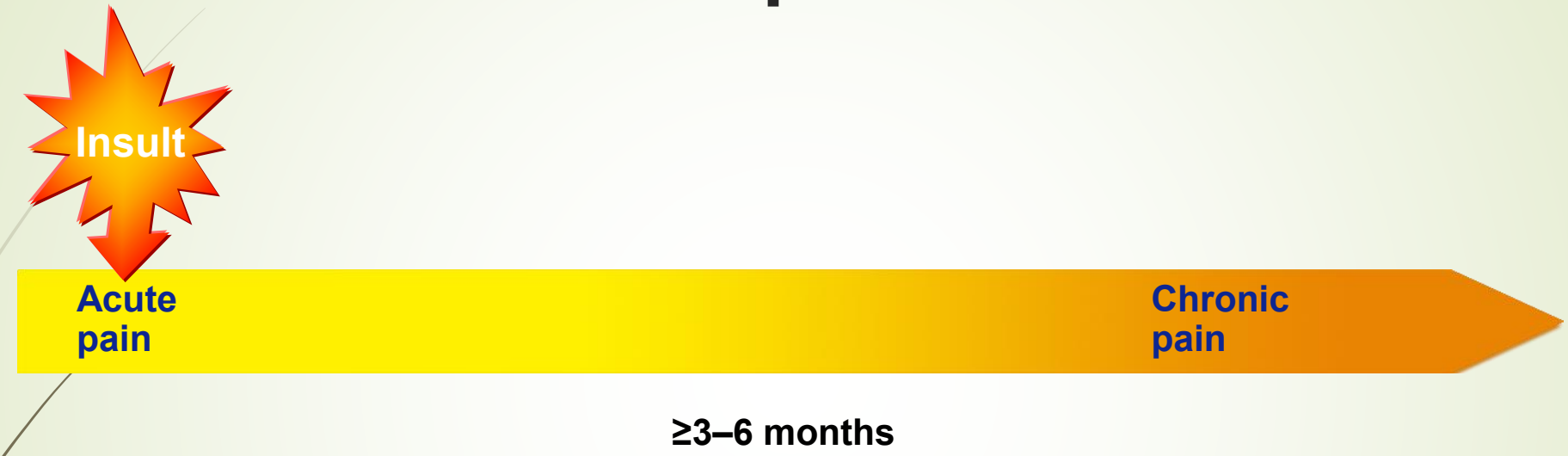
You want this to happen.

Bad Inflammation (Chronic)

Long-term response that happens when the fire alarm gets stuck and never turns off. Immune problems, stress, poor diet, or toxins.

Constant attack damages healthy cells.

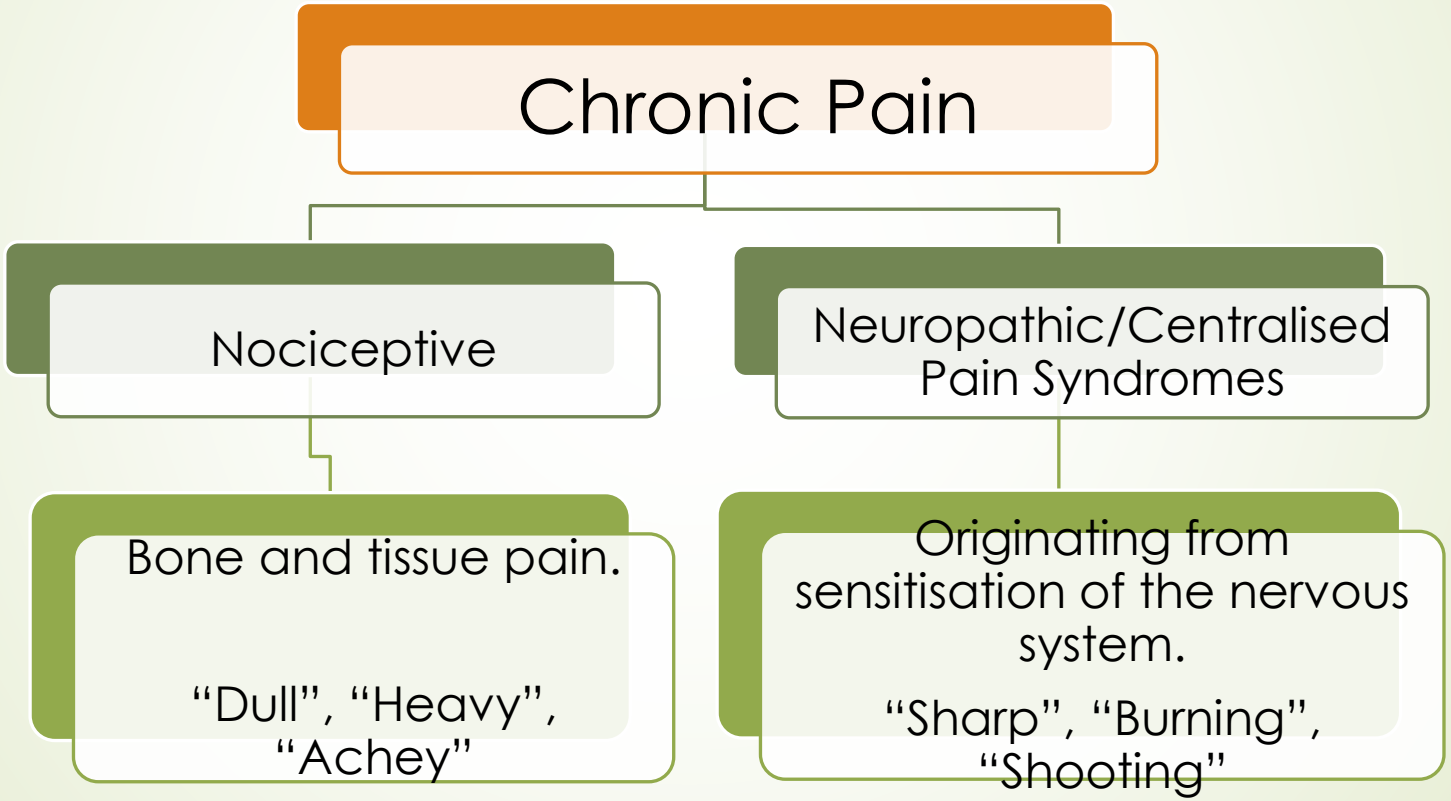
The continuum of pain



- Serves a protective function
- Resolves on healing

- Serves no protective function
- Degrades health and function

We identify 2 main types of chronic pain:



Types of Pain continue:

Nociceptive pain
(inflammatory)

- Somatic
- Visceral

Neuropathic pain

- Central (brain, spinal cord)
- Peripheral

Mixed (ie Spine, Cancer, CRPS)

NOCIPLASTIC (3rd type):
Widespread/ Central Sensitisation

CHEMICALS INVOLVED

(Mast-cell-derived mediators)

Histamine

Tryptase,

Prostaglandin D_2 (PGD_2)

Leukotrienes (especially LTE_4)

Heparin,

Various cytokines and chemokines.

The core idea:

mast-cell mediators turn up the “volume” on pain nerves

Mast cells sit right next to sensory nerves.

When activated, they release chemicals that:

- lower the activation threshold of pain fibres
- cause local inflammation
- promote nerve sprouting and hypersensitivity
- amplify signals in the spinal cord and brain

This is why MCAS pain can feel burning, aching, stabbing, or migratory.

1. Histamine — directly excites pain nerves

Histamine acts on **H1 and H4 receptors** on nociceptors (pain-sensing neurons).

Effects:

- **Direct activation** of C-fibres → burning, itching, stinging
- **Peripheral sensitisation** → nerves fire more easily
- **Central sensitisation** via spinal cord histamine receptors
- **Vasodilation + swelling** → mechanical pressure on nerves

2. Prostaglandin D_2 (PGD_2) — amplifies inflammatory pain

PGD_2 is a potent inflammatory mediator.

It contributes to pain by:

- sensitising nociceptors through prostaglandin receptors
- increasing blood flow and swelling
- enhancing the effect of histamine and bradykinin
- promoting central sensitisation

This is similar to how prostaglandins drive menstrual or injury-related pain.

3. Leukotrienes (especially LTE_4) — cause deep, cramping, and visceral pain

Leukotrienes:

- cause smooth-muscle contraction → abdominal cramping
- increase vascular permeability → swelling around nerves
- activate leukotriene receptors on sensory neurons

This is why leukotriene blockers (e.g., montelukast) sometimes reduce MCAS-related pain

4. Tryptase — activates PAR-2 receptors on nerves

Tryptase is one of the most pain-relevant mast-cell enzymes.

It:

- activates **PAR-2 receptors** on nociceptors
- promotes **nerve sprouting**
- increases long-term hypersensitivity
- contributes to neuropathic-type pain

PAR-2 receptors (Protease-Activated Receptor 2) are cell-surface proteins that act as biological alarms

PAR-2 activation is strongly linked to chronic widespread pain, including fibromyalgia-like symptoms.

5. Cytokines (IL-6, TNF-α, IL-1β) — drive chronic, deep, aching pain

These cytokines:

- maintain long-term inflammation
- increase spinal cord excitability
- impair mitochondrial function → fatigue + pain
- promote hyperalgesia (increased pain from painful stimuli)
- promote allodynia (pain from normally non-painful stimuli)

This is the “flu-like” pain many MCAS patients describe.

IL= Interleukin TNF= Tumor Necrosis Factor

6. Nerve growth factor (NGF)

— increases nerve density and sensitivity

Mast cells release NGF, which:

- causes **nerve sprouting**
- increases the number of pain receptors
- maintains chronic pain states

This is a major contributor to persistent, widespread pain.

7. Platelet-activating factor (PAF)

— contributes to severe, burning pain

PAF:

- activates nociceptors
- increases vascular permeability
- amplifies inflammatory cascades

It is implicated in severe flares and anaphylaxis-like episodes.

Putting it together: why MCAS pain is so varied

Each symptom is linked to the mediators most strongly associated with it

- **Histamine** → itching, burning, flushing, nerve firing
- **Tryptase / PAR-2 activation** → neuropathic, electric, stabbing pain
- **Prostaglandin D_2 (PGD_2)** → throbbing, vascular, inflammatory pain
- **Leukotrienes** → cramping, visceral pain
- **Cytokines (IL-6, TNF-α, IL-1β)** → deep, flu-like, widespread pain
- **NGF** → nerve sprouting, chronic widespread pain

MEDICATIONS THAT TARGET MAST-CELL GENERATED PAIN

Pain Symptom	Likely Pathways	Treatment Categories That Align
Burning	Histamine, tryptase, nerve sensitisation	Histamine support, mast-cell stabilisation, neuropathic-pain approaches
Stabbing/electric	Tryptase, NGF, central sensitisation	Mast-cell stabilisation, neuropathic-pain approaches
Deep aching	Cytokines, prostaglandins	Anti-inflammatory support, prostaglandin support
Throbbing/migraines	PGD_2, histamine	Prostaglandin support, histamine support

Pain Symptom	Likely Pathways	Treatment Categories That Align
Cramping gut pain	Leukotrienes, histamine	Leukotriene support, histamine support
Widespread pain	NGF, cytokines, tryptase	Mast-cell stabilisation, anti-inflammatory, neuropathic-pain approaches
Skin allodynia	Histamine, tryptase, NGF	Histamine support, mast-cell stabilisation, neuropathic-pain approaches

Category	Medication	Purpose	Primary Care Prescribable?
H1 blockers	Cetirizine	Reduce histamine effects	Yes
H2 blockers	Famotidine	Manage gastric symptoms	Yes
Leukotriene blockers	Montelukast	Address leukotriene effects	Yes
Mast cell stabilisers	Sodium cromoglicate	Prevent mediator release	Yes
Mast cell stabilisers	Ketotifen	Prevent mediator release	Yes
Corticosteroids	Prednisolone	Reduce inflammation symptoms	Yes
Bioflavonoids	Quercetin	Natural mast cell stabilisers	OTC
Vitamins	Vitamin C, Vitamin D, Probiotics, Magnesium	Support stabilising mast cells, control histamine levels & histamine production	OTC
Emergency medication	Adrenaline	Anaphylaxis management	Yes
	Low Dose Naltrexone	Mast cell stabilisers	No *

Onward referral to secondary care

- if symptoms are severe,
- significantly impact daily life
- do not respond to first-line treatments
- if specialist input is needed for further diagnostic evaluation and management daily

Treatment typically follows a stepwise approach:

- starting with H1 and H2 antihistamines,
- followed by mastcell stabilisers,
- leukotriene receptor antagonists,
- other adjuncts as needed.

Dosing is often individualised, with some patients requiring higher-than-standard doses for symptom control.

SUPPLEMENTS

1. Mast-cell stabilisers

These are the supplements most often associated with calming mast-cell reactivity.

- **Quercetin** Helps stabilise mast cells and may reduce release of histamine, leukotrienes, and cytokines.
- **Luteolin** Similar to quercetin but sometimes better tolerated; supports mast-cell stability.
- **Rutin** A flavonoid that may support histamine balance and mast-cell regulation.
- **Perilla seed extract** Contains rosmarinic acid, which may help reduce histamine release.

2. Histamine-related pathways

These supplements are often discussed for supporting histamine breakdown or balance.

- **Vitamin C** Supports histamine metabolism and may reduce histamine levels.
- **Vitamin B6** Involved in histamine breakdown pathways.
- **Copper + Vitamin C balance** Copper is part of the DAO enzyme system, though this is a complex pathway and varies by individual.
- **DAO enzyme supplements** These are sometimes used to support dietary histamine breakdown.

DAO=Diamine oxydase

3. Cytokine and inflammatory pathways

These may help with deep, aching, or flu-like inflammatory symptoms.

- **Omega-3 fatty acids (EPA/DHA)** Support anti-inflammatory signalling.
- **Curcumin (from turmeric)** Often discussed for its anti-inflammatory properties.
- **Boswellia** May help reduce inflammatory signalling.

4. Leukotriene-related pathways

These supplements may influence leukotriene production or signalling.

- **Omega-3 fatty acids** Can shift the balance away from leukotriene-driven inflammation.
- **Perilla seed extract** Contains compounds that may influence leukotriene pathways.

5. Oxidative stress and mitochondrial support

These can be relevant because oxidative stress can trigger mast-cell activation.

- **N-acetylcysteine (NAC)** Supports glutathione production.
- **Alpha-lipoic acid** Supports antioxidant pathways.
- **CoQ10** Supports mitochondrial function.

Oxidative stress =imbalance between unstable molecules called free radicals and antioxidant defenses in your body

Glutathione = powerful antioxidant naturally produced by your body's cells. Essential for neutralizing free radicals, supporting liver detoxification, and maintaining cellular health.

Mitochondrion (plural: mitochondria):primary function is to generate adenosine triphosphate (ATP), which serves as the cell's main chemical energy currency

6. Gut-related support

The gut is a major mast-cell hub, so supplements that support gut balance could be considered.

- **Probiotics (strain-specific)** Some strains may support gut barrier function, though tolerance varies widely.
- **Glutamine** Supports gut lining integrity.
- **Aloe vera (inner leaf)** Sometimes used for soothing gut irritation.

TRADITIONAL PAIN MEDICATION

MEDICATION

ANALGESIA

- Paracetamol
- Anti-inflammatory drugs (NSAIDs)
- Opioids (weak to strong)

ADJUVANT DRUGS

- Tricyclic antidepressants
- Dual acting antidepressants
- Anti-epileptic drugs
- Topical drugs

NEUROPATHIC PAIN DRUGS

NICE (Primary Care, adults)

4 equal

Amitriptyline (TCAD), **Duloxetine** (SNRI)
Gabapentin & **Pregabalin**

Single drug, rather than combining

Trigeminal neuralgia: carbamazepine

How traditional pain medicines interact with mast-cell biology

1. Medicines that are *often better tolerated*

These tend to have **neutral or calming effects** on mast-cell pathways.

Paracetamol

- Generally considered neutral on mast cells.
- Often used for headaches, mild pain, or fever.
- Does not significantly affect histamine, prostaglandins, or leukotrienes.

Certain neuropathic-pain medicines

These don’t act on mast cells directly but target nerve hypersensitivity, which is common in MCAS.

They may help with:

- burning pain
- electric or stabbing pain
- allodynia (pain from light touch)
- widespread nerve sensitisation

(Histamine, Tryptase, NGF sensitise nerves)

2. Medicines that can be *helpful but require caution*

These interact with mast-cell pathways in more complex ways.

Anti-inflammatory medicines (non-salicylate types ie ibuprofen, diclofenac, naproxen)

- Reduce prostaglandin-driven pain.
- Some people with MCAS tolerate them well; others find they trigger symptoms.
- Sensitivity varies because prostaglandins and leukotrienes are tightly linked in mast-cell chemistry.

Low-dose salicylate-type medicines (aspirin= acetylsalicylic acid)

- Reduce prostaglandin D_2 (PGD_2), a major mast-cell mediator.
- Can help with flushing, vascular headaches, and inflammatory pain.
- But some people are sensitive to salicylates, so responses differ widely.

3. Medicines that can *trigger mast-cell activation* in some people

These are not “bad,” but they are known to cause mast-cell degranulation in certain individuals.

Opioid-type pain medicines

- Some can directly trigger mast-cell degranulation.
- This can lead to itching, flushing, hives, or worsening pain.
- Sensitivity varies by individual and by specific medicine.

Certain muscle relaxants

- Some can cause histamine release.
- Others are neutral.
- Responses are highly individual.

4. Why MCAS changes the way pain medicines work

MCAS pain is often a mix of:

- inflammatory pain
- neuropathic pain
- vascular pain
- visceral (gut) pain
- widespread cytokine-driven pain

Traditional pain medicines usually target **one** of these pathways, while mast-cell mediators activate **several** at once.

That's why:

- some people feel little relief
- some feel worse
- some respond only when mast-cell stabilisation is added
- some need a combination of approaches

5. The most important principle:

Pain control in MCAS works best when the mast-cell activation itself is addressed.

Traditional pain medicines can help, but they often work better when combined with:

- mast-cell stabilisation
- histamine pathway support
- prostaglandin/leukotriene pathway support
- gut-related support (if symptoms are GI-driven)

This is because the underlying driver of the pain is often the mediator release, not just the pain signal itself.

NON-PHARMACOLOGICAL WAY OF MANAGING MCAS and PAIN

1. Avoid Specific Triggers

- Track reactions with a **symptom and food diary** to find your exact triggers.
- Protect yourself from environmental triggers like **harsh chemicals, perfumes, and extreme temperatures**.
- Locate household irritants—for example, ensure pet litter boxes are far from living areas.

2. Follow a Low-Histamine Diet

- **Histamine** is a chemical that causes allergic symptoms.
- Eat fresh foods immediately; avoid fermented, aged, or leftover foods.
- Limit high-histamine items like **aged cheeses, cured meats, spinach, and tomatoes**.
- Work with a registered dietitian to create a safe meal plan.

3. Manage Your Routine and Energy

- Keep a **consistent daily schedule** for eating, sleeping, and waking up.
- Practice **pacing** by balancing your activities and resting before you feel tired.
- Prevent **post-exertional malaise** (the extreme tiredness after doing too much).

4. Regulate the Nervous System

- Stress releases chemicals from mast cells, making MCAS symptoms worse.
- Calm your body using deep breathing, **mindfulness**, or meditation.
- Avoid overexertion by spacing out daily tasks and tracking your baseline energy.

MANAGE THE PAIN FROM THE CO-OCCURING CONDITIONS

Chronic Migraine

Acute attack, preventative

Headache Clinic referral?

Ehlers-Danlos Syndrome

Joint stabilisation—specialist physiotherapy

Enabling equipment

Orthoses, joint supports

Gastro-intestinal Issues:

Constipation and evacuation management

IBS management

Reflux

Gastroparesis

Dietetic management

Bladder and Pelvic Floor

Interstitial cystitis: Bladder instillations

Pelvic Floor physiotherapy

Avoid Bladder irritant food and drink

Continence management

Immune Conditions: Rheumatology

Physical methods of Pain relief

- TENS
- Acupuncture
- ICE
- Massage
- Vagus Nerve Stimulation

IMPORTANT CONSIDERATIONS

- **Individual Variability**: What works for one patient may not for another, and sometimes, many different therapies must be tried.

- **Medication Sensitivity**: MCAS patients can react to medications, including preservatives and fillers in tablets, so compounded medications may be necessary.

- **Medical Supervision:** Treatment should be closely managed by a knowledgeable specialist to avoid triggering anaphylaxis

ONE NEW THING AT A TIME! GO LOW, GO SLOW

THANK YOU

https://www.mastcellaction.org/

https://www.kentcht.nhs.uk/service/community-chronic-pain/

https://www.mastcellaction.org/assets/_/2026/07/07/79b651ac-3658-4686-9541-db26f366ddf1/final-primary-care-guide-2026.pdf?v=1