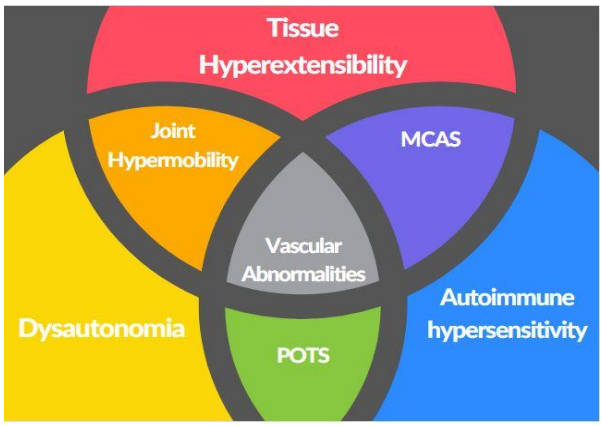
Clinician Guide: Constellation of Chronic Medical Conditions Commonly Seen in Autistic & ADHD Adults

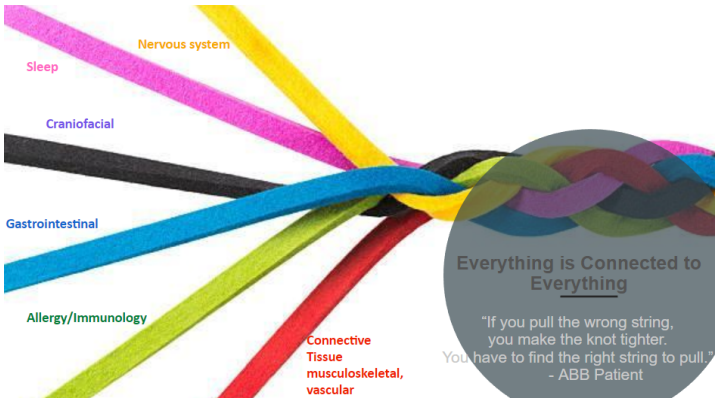
This resource is intended as an introductory primer for primary care clinicians who are beginning to consider whether a patient's component conditions are **part of a larger constellation**. The relationship between Autism/ADHD and these conditions is well-established in the literature, and is linked throughout this resource. There is also literature identifying sub-clusters amongst these conditions, including hypermobility, dysautonomia, chronic pain, neurodivergence (Csecs et al 2022); hypermobility, dysautonomia, GI, allergic conditions (Brooks et al 2021), and hypermobility, dysautonomia,mast cell dysfunction (Wang et al 2021). We expect that this resource may be useful for many of your non-Autistic/ADHD patients.

The main goals of this introductory resource is to emphasize the connections between these medical conditions, and explain how these connections may impact management (and hinder clinical improvement).

1. For patients with this constellation who are not improving, consider screening for the rest of the constellation.
2. In the Management table, we think the most important part is the "Cautionary Notes" column. Th ese may reveal unrecognized barriers to clinical improvement. **Many of the standard treatments for some components of the constellation make the other component conditions worse.**

*We have included many references including those authored by the many clinical experts on these topics. We also note that **Dysautonomia International** and **The Mast Cell Disease Society** have* been invaluable to our own learning.





PREVIEW: Examples of medical conditions that belong to this constellation:

- Hypermobility spectrum disorder / hypermobile Ehlers-Danlos
- POTS / Dysautonomia
- Irritable bowel syndrome
- Chronic pain / Fibromyalgia
- OSA
- ME/CFS
- Migraine
- Vitamin deficiencies
- Metabolic disorders
- Long COVID
- Mast cell dysfunction / mast cell activation syndrome / mast cell activation disease

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Autism/ADHD commonly co-occur with many other brain-related differences outside the scope of this project. There are MANY other aspects of improving healthcare for neurodivergent patients that fall outside the scope of this project. **To access additional education from All Brains Belong VT, visit https://allbrainsbelong.org/education**

Part 1. Evaluation

Of note, many patients have had symptoms for decades, and may not think to bring these up - particularly if the symptoms have been normalized intergenerationally. Many neurodivergent patients do not identify with standard Review of Systems terms; click to read words our focus group participants used to describe their symptoms.

Conditions	Key Elements of History	Exam/Testing/Screening
Sleep disorders • Obstructive sleep apnea (OSA) • Upper airway resistance syndrome (UARS) • RLS / sleep movement disorders • Other sleep disorders *Further reading:* • ADHD & Sleep disorders • Sleep disturbances in Autism • Autism & OSA • ADHD & OSA • EDS & OSA • Autism & RLS	• Daytime fatigue / sleepiness • +/- snoring • Frequent awakenings • Unrefreshing sleep • Morning headaches • +/- teeth grinding / TMJ • Nocturia not otherwise explained • Nightmares • Sleeps better in an upright position / in a chair • Heavy labored breathing during sleep, "trying to breathe thru a straw" • Nocturnal HTN • "3am wakeups" (known to be linked to histamine, may indicate MCAD)	• Refer to Sleep Medicine • Consider polysomnography • Screen for other potential co-existing disorders in this guide Notes: • 30% of patients with OSA have normal BMI • In our practice of autistic / ADHD adults who have undergone PSG, zero have had normal studies.
Hypermobility spectrum disorder (HSD) / Hypermobile Ehlers-Danlos syndrome (hEDS) *Further reading:* • Autism and EDS • Comorbidities in EDS • EDS comorbidities research poster • ADHD & hypermobility • Prevalence of ADHD and Autism Spectrum in Hypermobility • Hypermobility, ND & Pain • Neurological & Spinal Manifestations of EDS	• Life-long chronic pain (often since childhood) • Wide range of connective tissue symptoms, including: hyperelastic skin, tissue fragility, easy bruising, poor skin healing, dislocations/ subluxations or "joint popping," early-onset varicose veins, gingival recession, easy bleeding gums • FHx of aneurysms, dissections, other connective tissue related sx • May have fibromyalgia or chronic pain diagnosis • Weak postural support, "sits like a pretzel" • Repetitive injuries, injuries with mild mechanism (sitting on a hard bench, carrying a heavy bag) • May have tight musculature to compensate for ligamentous laxity	• **PCPs can diagnose EDS**! See EDS Society diagnostic checklist • How to perform a Beighton score - keep in mind that this score does not include proximal large joints (spine, hips, etc) • Hypermobility is a spectrum disorder- may not check "all the boxes" • Imaging not usually helpful unless suspicion for cervical instability • If clinical suspicion of vascular type of EDS, consider referral for genetic counseling/ tests (not needed for hEDS) • Screen for co-existing disorders (dysautonomia, OSA, MCAD, etc)

Conditions	Key Elements of History	Exam/Testing/Screening
Cardiovascular • POTS / dysautonomia *Further reading:* • Hypermobility & dysautonomia • Dysautonomia in hypermobility • POTS & EDS • Dysautonomia International: POTS for Clinicians • Autism & POTS • MCAS & POTS • Autoimmunity & POTS • Concussion & POTS	• Dizzy upon standing, tachycardia / palpitations upon standing • Recurrent presyncope/syncope • Exertional dizziness, fatigue, and/or brain fog (during or after) • Patients describe "brain fog" in many ways - cloudy, word-finding/ memory difficulties, drowning, hazy • Dizziness/presyncope with temperature changes (hot showers, hot weather), barometric pressure, positional changes • Dysequilibrium / chronic vestibular symptoms • Fingers / toes "feel cold easily" • Lower extremities turn red / purple with standing (venous pooling), particularly in heat / shower • HA with exertion / temp changes • Excessive or reduced sweating • Photophobia (related to CN3) • Tinnitus or visual changes • May be misdiagnosed with anxiety and/or panic	• Modified 10 minute standing test or NASA 10 Minute Lean Test (can do in your office) - may need to repeat when symptomatic • Tilt-table test with caution • **Clinical hx often sufficient** to initiate trial of lifestyle changes-salt, compression, fluids • Orthostatic vital signs • BP response will depend on type of dysautonomia, • Consider OSA evaluation • Close monitoring for worsening under conditions of stress, concussion, surgery, pregnancy, infection, etc. • Eval for autoimmune disease, including Hashimoto's thyroiditis, RA, Ankylosing spondylitis
Allergy / Immunology • Allergic rhinitis • Asthma • Chronic urticaria • **Mast Cell Activation Syndrome (MCAS) / Mast Cell Activation Disease (MCAD)** • Autoimmune disease - including Hashimoto's, Sjogren's, RA, SLE) *Further reading:* • Allergies, asthma & autism • Allergic conditions & ADHD • Autoimmune disease & autism • Autoimmune genes & autism See next page for mast cell disease reading list	MCAS / MCAD is a surprisingly common condition connected with symptoms in a wide range of organ systems.Mast cell dysfunction is broader than systemic mastocytosis. Most clinicians did not receive training in MCAD. Recommended reading: • **Often seen, rarely recognized: mast cell activation disease--a guide to diagnosis & therapeutic options** (Afrin et al 2016) • **Characterization of MCAS** (Afrin et al 2018) - we call your attention also to Table 2 with sx summary) Mast cell dysfunction is connected to MANY chronic medical conditions that you may already know a patient has, including • Prediabetes & type 2 diabetes • NAFLD/NASH • Interstitial cystitis • Osteoporosis • Many more	Validated Questionnaire to recognize symptoms (Afrin & Molderings, 2014) Most frequent physical exam findings MCAS Dx criteria: 1) Symptoms in 2+ organ systems 2) Symptoms improve with antihistamines or other mast cell-targeted treatments 3) Mast cell mediators seen on labs Lab tests (algorithm) • See next page for cautionary notes. • Consider empiric treatment if testing is too costly or otherwise difficult to obtain.

<table>
<tr>
<td>MCAD (continued….)

<u>Further reading:</u>
• Often seen, rarely recognized: mast cell activation disease--a guide to diagnosis & therapeutic options
• Characterization of MCAS
• Mast cells and Autism
• Mast cells and hypermobility
• Mast cells & ADHD
• Hypermobility, Mast cells, and Ig deficiency
• Mast cell activation: beyond histamine & tryptase</td>
<td colspan="2">Notes about evaluating for MCAD / mast cell dysfunction:
While lab tests are required for a formal “MCAS” diagnosis, most patients with mast cell dysfunction in primary care will have normal lab tests. We recommend specifically preparing patients for this to set expectations, if testing is ordered. Patients with normal MCAS labs may still respond to mast cell targeted tx.

Difficulties with testing:
- Many mast cell mediators act locally (with insufficient systemic levels to be measured in blood or urine tests)
- Many have very brief half lives, requiring testing within hours of onset
- Difficult to assure proper lab specimen handling - plasma must be kept cold (including cold centrifuge) then frozen; urine must also stay cold
- Many insurance carriers do not cover these tests - CPT codes should be individually checked with an insurer

If available, lab workup can include: serum tryptase (85% of MCAS patients have a normal tryptase – but still have MCAS!), Chromogranin A, Plasma histamine, 24-hour AND spot urine collections for N-methylhistamine, 2,3 dinor 11-beta-PGF2-alpha, leukotriene E4

Consider referral to Hematology or Immunology with specific MCAS expertise

Other work-up to consider:
• SIBO testing vs. empiric treatment
• Consider testing for HAT (hereditary alpha-tryptasemia)
• GI workup for eosinophilic esophagitis
• If having biopsy - CD 117 stain (normal < 20/hpf). GI bx should be from proximal duodenal bulb or terminal ileum</td>
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<tr>
<td>Gastrointestinal disorders
• IBS (diarrhea or constipation)
• Celiac disease
• Food sensitivities/ intolerances
• Gastric motility disorders

<u>Further reading:</u>
• GI Conditions & Autism
• Adult Autism & GI
• Functional GI disease & Autism
• Celiac disease & autism
• hEDS & dysmotility
• POTS & GI Conditions
• MCAS Primer for the Gastroenterologist
• Eating-related challenges & autism
• Bladder & bowel dysfunction in Autistic adults</td>
<td>Beyond standard history for GI conditions belonging to this constellation, Autistic & ADHD patients disproportionately report:
• Nausea, satiety, abdominal pain - before, during, or after eating
• Low or high stomach acid
• Disordered eating and/or other related challenges
• Food aversions
• ARFID
• Difficulty swallowing, "lump in throat, choking/gasping/gagging with eating and drinking
• Difficulty with high fat foods
• Chronic diarrhea or constipation, large caliber stools
• Frequent reactions to food, even seemingly implausible
• Pain, nausea, fatigue after eating
• Early onset or refractory GERD
• Excessive eructation (burping)</td>
<td>• anti-TTG and total IgA
• Evaluate for H.pylori
• Consider GI referral
• While controversial, there is growing evidence for exploring gut dysbiosis - consider SIBO eval and/or methane breath test
• Consider impaired nutrient absorption
• Consider MCAD
• Also higher rates of eosinophilic esophagitis in this population, which is independently correlated with ARFID</td>
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Conditions	Key Elements of History	Exam/Testing/Screening
Chronic pain & related conditions - examples: • Fibromyalgia • Migraine • Small fiber neuropathy • Raynaud's disease *Further reading:* • Pain, hypermobility, Autism • Joint hypermobility links Neurodivergence to Dysautonomia and Pain • Autism and central sensitivity • Fibromyalgia & Adult ADHD • Autism & migraine • SFN & Fibromyalgia • SFN & Post-COVID • PPPD & migraine • Autonomic dysfunction & concussion	• Chronic Pain • Pain "everywhere," "all the time" • Post-exertional malaise • Pain out of proportion to injury or condition • Altered pain tolerance • Pain with temperature changes or compression in Raynauds Patients with this constellation may already carry dx of functional neurologic disorder Of note, patients with this constellation of medical conditions also commonly meet criteria for ME/CFS. Pain exacerbated with activity may be a component of "post-exertional malaise" (PEM) - see below. Many patients with this constellation also have non-specific vestibular symptoms (ie "dizziness" that are multifactorial in etiology. Patients with diagnoses such as post-concussion syndrome, cervicogenic dizziness, persistent postural-perceptual dizziness (PPPD), post-concussive dysautonomia etc may benefit from managing the constellation as a whole.	Fibromyalgia: Formal Dx Criteria Review (NIH) likely outdated SFN evaluation Screen for other potential co-existing disorders on this table, including EDS and MCAD Screen for vitamin deficiencies, which may be present even if testing normal; particularly if co-occurring POTS- may have decreased blood volume and thus relative hemoconcentration. • Vit D, iron, magnesium • B12* *Note: B12 can be falsely elevated in inflammatory states; there can also be intracellular deficiency or genetic metabolic variations that impact one's ability to utilize B12* . If vestibular sx, consider visual function assessment, including for dominant parvocellular visual pathway and convergence issues If headaches/dizziness with prolonged upright posture, consider eval for CSF leak, which are more common in EDS
Post-infectious chronic illness & related conditions: • Long COVID • ME/CFS *Note: the existence of post-infectious chronic illnesses is not new* *Further reading:* • Post-Covid & MCAS • Mast cells & COVID • Impact of COVID on autistic patients • COVID, Autism & melatonin deficiency	• Chronic fatigue, malaise, headaches, brain fog, pain • Started *during/after* illness (ie, C19, EBV, Lyme), toxic exposure, TBI • Unrefreshing sleep, chronic fatigue • Post-exertional malaise (PEM) • Orthostatic intolerance • Symptoms are new or worsened by infectious illness and continue past acute/subacute period • New or worse reactions to new unknown or known triggers (food, chemicals, environment, etc.) • Fibromyalgia-like symptoms • Unexplained neuropathy • Chronic flu-like sx: ie., sore throat, headaches, low-grade fever, chills, lymphadenopathy	• See: Mayo Clinic Guidelines for ME/CFS • Testing not usually helpful • Consider co-existing MCAD • Screen for other potential co-existing disorders (OSA, dysautonomia) • Screen for vitamin deficiencies as above

Conditions	Key Elements of History	Exam/Testing/Screening
Reproductive • Endometriosis • PCOS • PMDD • Low-testosterone (for age) • Congenital adrenal hyperplasia (CAH) *Further reading:* • Reproductive symptoms & EDS • Endometriosis & migraine • Mast cells & endometriosis • Endometriosis & adenomyosis • Autism & PCOS • ADHD & PCOS • ADHD & PMDD • Autism & PMDD • ADHD & testosterone • Autism & CAH • Reproductive Health, Long COVID, Connective Tissue Disorders, POTS & ME/CFS	Patients commonly experience mast cell mediated cyclical triggers in response to hormone shifts. This includes: • Perimenstrual mood, migraine, pain & digestive symptoms • Dysmenorrhea • Symptom flares in response to menopause or beginning or adjusting gender affirming hormone treatment Recurrent miscarriages (self or family history) are common in this population, likely related to increased prevalence of MTHFR mutations. • Autism & MTHFR • Recurrent pregnancy loss & MTHFR	In addition to standard workup (Endometriosis, PCOS, PMDD, low-testosterone for age), consider: Our approach for patients with the big picture of this constellation: • If Assigned Female at Birth, consider TVUS if indicated • Screen for co-existing MCAD *Note*: differences in hormone regulation are incompletely understood and/or taught in standard medical education, (e.g. systemic effects of stress thus cortisol levels from development through adulthood, or menstrual hormonal shifts and the relationship to mast cell dysfunction, only to name a few).
Craniofacial / Skull / Dental • Temporomandibular dysfunction • Ankyloglossia • Periodontal disease (related to collagen abnormality) *Further reading:* • Mast Cells & Periodontitis • Mast cells & Gingival Inflammation • Atypical odontalgia, Autism & ADHD • TMD & EDS • Autism & oral health • Autism & craniofacial signs • Chiari malformation & EDS	• History of tongue tie • TMJ symptoms / history • Grinding teeth • Cracked teeth • Significant pediatric dental caries • Bruxism • High arch palate, teeth crowding - palate expander earlier in life • Head tilted to one side - vestibular, neck muscle tightness from breathing mechanics, visuomotor dyspraxia • Teeth continue to move past puberty (including in adulthood) • Teeth more likely to “move back” (even with retainers, etc.) • Molars have "high cusps and low fissures," increasing risk of cavity • See also: EDS Oral Manifestations	• Oral tethers - tongue, lip • Screen for co-existing conditions • Low threshold for sleep study • Consider role of TMJ in chronic neck pain and headache

MANAGEMENT

This resource is intended as an introductory primer for primary care clinicians who are beginning the process of zooming out to further characterize their autistic and/or ADHD patients' multi-system medical conditions that may be representative of the constellation described in this project. The purpose of considering whether a patient's component medical conditions are part of a larger constellation is that this may impact medical management (as discussed in Table 2).

We have organized the table by system and list specific representative disorders by name for ease of reference. However, it is important to note that the main idea of this project is that this population often experiences these conditions as a constellation.

For every system of conditions, we recommend considering whether any and all of the other system's conditions are present or not.

- For example, this population commonly experiences mast cell dysfunction. Managing the mast cell dysfunction would be expected to improve the sleep disorder, the GI disorder, the POTS, the chronic pain, etc.
- Likewise, poorly controlled dysautonomia and/or chronic pain and/or any inflammatory condition may worsen mast cell dysfunction because of autonomic nervous system impact on mast cells. Poorly controlled GI disorders may impact absorption of medications and supplements.

For all of these reasons, we recommend thinking about these conditions as one constellation.

Note: Because MCAD is so common in this population, this may be a particularly helpful lens to think through.

Recommended reading:

- **Often seen, rarely recognized: mast cell activation disease--a guide to diagnosis and therapeutic options** (Afrin et al 2016)
- **Characterization of MCAS** (Afrin et al 2018) - we call your attention also to Table 2 with symptom summary)

As noted above, Autism/ADHD commonly co-occur with many other brain-related differences outside the scope of this project. There are MANY other aspects of improving healthcare for neurodivergent patients that fall outside the scope of this project. **To access additional education from All Brains Belong VT, visit https://allbrainsbelong.org/education**

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Sleep disorders • OSA/UARS • RLS *Further reading:* • Sleep disorders in ADHD • Melatonin in chronic sleep disorders & autism • ADHD low ferritin & RLS • Iron & RLS • Melatonin in autism	Optimize management of MCAD *plus* -UARS • Nasal airway hygiene (i.e., nasal saline, humidification) • Manage allergic rhinitis • Particularly if co-occurring hypermobility, patients with connective tissue disorders have higher rates of mechanical airway collapse - consider Breathe Right(™) strips • Address postural support - elevate head of bed, work with PT re supportive positions / pillows for sleep (often requires extensive trial & error) -OSA: CPAP, in addition to the above -RLS • In addition to standard management, supplemental iron (target ferritin target >75)[1] • Treatments under investigation: Vit D, magnesium and Vit B6 -Insomnia • Beyond standard management, consider melatonin (0.5-3 mg) given higher rates of melatonin disturbance in this population • Consider L-theanine (50-200 mg) given decreased GABA levels in autism	Hypnotics and muscle relaxants may worsen airway obstruction in the setting of hypermobility / hyperextensible airway soft tissue Cannabis use may worsen airway obstruction secondary to drying mucous membranes *CPAP considerations* • Mouth-breathers require a full face mask • Seal is essential, air leaks may worsen inflammatory dry eye and/or increase risk of corneal abrasions for patients with hEDS. • Patients may have mast cell reactions to adhesive of breathe right strips (try other brands) or silicon CPAP masks Often patients are taking a supratherapeutic dose of melatonin.This may result in poor efficacy and/or side effects. This particular population benefits from low doses 0.5-3 mg. We discourage use of quetiapine or other atypicals for insomnia. Dopamine antagonism may have a disproportionate adverse impact in Autism/ADHD.(Certainly for psychosis or mania, benefits may outweigh risks – but this is not the case for insomnia) .

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Hypermobility spectrum disorder & Hypermobile EDS *Further reading:* • Hypermobile Ehlers-Danlos Syndrome • Examination and Treatment of a Patient With Hypermobility Syndrome • 2017 EDS International Classification • Perioperative & Anesthesia Management for hEDS • Visual Manifestations of EDS	Multi-disciplinary approach. Prioritize referrals to hypermobility-informed allied health professionals (e.g. PT, OT, myofascial therapist, coach, etc) • Focus on stabilizing large joints • Educate on injury prevention including body mechanics and braces for joint protection • Frequent repositioning - for both pain and pressure injury prevention • Postural supports for work station, bed, car Craniocervical instability (CCI) is likely relatively common in h-EDS/HSD and often can be conservatively managed with PT, though in rarer cases the presence of red flags can indicate the need for prompt specialist referral. Screen for GU/GI problems (i.e, urinary incontinence, constipation, pelvic organ prolapse), which are common in this population - patients may not bring up. If present, pelvic PT is an essential component of management. Optimize management of mast cell dysfunction (mast cells communicate with connective tissue) and dysautonomia Consider sleep study (OSA is extremely common!) Consider screening echocardiogram and AAA screening via abdominal ultrasound. EDS patients may be at higher risk for valvular abnormalities, aortic root dilatation and/or aneurysms given connective tissue abnormalities See below for additional pain management strategies See additional management strategies by topic (EDS Society) Perioperative considerations: • Perioperative & Anesthesia Management for hEDS • List of perioperative considerations for patients with hEDS *Additional treatments under investigation* • Vitamin C (cofactor for cross-linking of collagen fibrils)	If possible, avoid: • Muscle relaxants (particularly at bedtime, given high co-occurrence with OSA), • "Traditional" PT or manual therapies focusing on releasing tension, deep pressure - risk of injury • Surgery, including typically low-risk surgeries • Vascular procedures • Drugs that interfere with hemostatic processes • QUINOLONES If cannot avoid surgery, ensure support for airway and craniocervical instability. Also need to balance postoperative compression (for edema management) vs. tissue ischemia in the setting of this connective tissue disorder. Avoid or limit roller coasters and bumper cars (high rates of CCI) This is a multi-system disorder - e.g. chronic constipation due to hyperelastic colon, so needs multi-system supports Certain patterns of activity or exercise may increase ME/PEM/POTS issues, so monitor and adjust type of exercise

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Cardiovascular ● POTS / dysautonomia ● Raynaud's disease *Further reading* ● Dysautonomia: A Forgotten Condition - Part 1 ● LDN in POTS ● Lifestyle Adaptations in POTS (Dysautonomia International)	Optimize MCAD management Encourage at minimum 64 ounces of caffeine/sugar free fluid intake per day, consumed in boluses (not sips) and at the same time as salt ● Salt - 3-5g/day from food and supplements ◆ Examples: LMNT, Normalyte, Salt Stick Vitassium, Klaralyte ◆ See cautionary notes re supplement ingredients ● Optimize magnesium and potassium ● Compression: Abd / high waist, pelvic / abdominal binders (i.e., hernia belts), compression shirts, water submersion) preferable to stockings. ● Educate on fall prevention- slow to stand. ● Assess postural supports / workstation ergonomic setup ● Given upright postural worsening of perfusion, some patients benefit from semi-recumbent positions during and/or after meals (caution given high rates of co-occurring hiatal hernias in hypermobile patients), smaller meals, maintain stable blood glucose ● Exercise can begin recumbent. Utilize pacing protocols to avoid post-exertional malaise ● Elevating head of bed 4-6" may expand blood volume by activating the renin-angiotensin-aldosterone system Meds: ● Optimize MCAD management ● Low-dose naltrexone (LDN) - DIY compounding: Naltrexone 50mg diluted in 50mL H20- started at 1mg, work up to 4mg ● Midodrine start 5 mg BID, can titrate…. ● Pyridostigmine 60 mg TID ● Stimulant (see caution) ● May need IV hydration Other considerations: ● Thiamine and other B vitamins (note commonly co-occurring methylation pathway problems) ● In our practice, many patients have found guanfacine ER 1-2 mg daily to be helpful for post-exertional pain mediated by dysautonomia	Caution with compression ● Not too tight to impact perfusion (i.e., "workout clothes" / leggings often better tolerated than "compression garments" ● May also worsen small fiber neuropathy (feet/legs) ● Standard compression socks can be too restrictive at the ankle - consider "Futuro energizing socks" Many patients do worse on beta-blockers (MCAD) ADHD caution - If there are, or you suspect there are, co-occurring hyperelastic vasculature / vascular problems, monitor for increased pain or brain fog on stimulants - may reflect vasoconstriction with cerebral hypoperfusion Many electrolyte supplements and vitamins contain ingredients known to trigger mast cell dysfunction, ie sugar, Stevia (also may worsen vasodilation), artificial flavoring Patients with chronic need for intermittent IV hydration may end up with a port. This patient population may be at higher risk of clotting (given the presence of other conditions that comprise this constellation), which should be taken into consideration. ● Mast cells & VTE ● MTHFR & VTE

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Allergy / Immunology In this resource, we will focus on **Mast cell activation syndrome (MCAS**). **Mast cell activation disorder (MCAD)**, but management concepts also apply to mast cell activation disease / mast cell dysfunction without MCAS/MCAD diagnosis by labs, in addition to the many conditions that are linked to mast cell dysfunction. *Further reading:* • Treatment for MCAS • The Mast Cell Disease Society • LDN in rheumatologic disease • Mast cells & inflammation	Common allergic / immunologic conditions in primary care (ie, allergic rhinitis, asthma, chronic urticaria) may benefit from considering MCAD. ADDRESS TRIGGERS The #1 intervention is to first address triggers - e.g. environmental factors (mold, pollen, heat, cold, temperature / humidity / barometric / sunlight intensity changes, vibration, nickel and other metals including dental appliances and fillings, chemicals, dyes, preservatives, medications (ex, beta blockers, muscle relaxants, ACE inhibitors, others - possibly also inactive ingredients or dyes in meds/supplements), infection, foods, gluten, lactose, yeast, high histamine foods, high starch foods, autonomic nervous system dysregulation PHARMACOLOGICAL MANAGEMENT (Molderings et al 2016) Summary of approach to treatment: Block chemical mediators released by mast cells and/or stabilize mast cells to release less. H1 blocker & H2 blocker BID • Usually start with non-sedating H1 but 1st generation H1 blockers that cross the blood-brain barrier (i.e., hydroxyzine) may be helpful with neurologic-predominant symptoms (i.e., brain fog) but monitor for unwanted side effects • H2 blocker added to H1 has synergistic effect on histamine regulation. Famotidine started at 20 mg BID, some patients may need 20 mg TID or 40 mg BID or higher • 2-4 week trial of a H1/H2 at a given dose, may need to try multiple H1s or multiple formulations - brand vs. generic vs. compounding pharmacy, gel vs. capsule vs. tablet; trial and error can be frustrating. Consider adding leukotriene inhibitor (may need BID dosing), cromolyn as mast cell stabilizer (oral, inhaled, topical)- see further notes bewlow, NSAIDs / ASA Consider LDN - dosing described in Dysautonomia section OSA/sleep mgt as above	Reserve Benadryl for rescue, not maintenance. Look for non-pink (dyes) version. Cromolyn is well recognized to have potential to worsen MCAD in first few days, lessens within 5 days. Can add extra antihistamines during these periods. “Odd” reactions to medications may actually be to fillers - may need to consider using a compounding pharmacy. Patients may also react to additives, coatings; may also be related to change of generic or brand or different manufacturer For patients with history of worsened neuroimmune symptoms after vaccination, consider antihistamines 1 hour prior to vaccination. Hormonal changes are a frequent trigger- monitor if starting HRT. Low H+ (as worsened by famotidine) may worsen dysautonomia related to H+/K+/ATPase pumps. However, poorly controlled MCAD also may worsen dysautonomia. It is common in this population to have Iron Deficiency with OR without anemia, sometimes requiring IV iron infusions. PO absorption may be limited by active GI mast cell disease.

MCAD (continued…)	Consider low histamine / anti-inflammatory diet (click here for examples) Decrease environmental exposures: ◆ Air purifier ◆ Window filters ◆ Assess for and treat mold in the house ◆ Pet exposure (consider no pets in the bedroom) ◆ Ensure adequate ventilation if indoor wood stove/fireplace ◆ Change clothing and shower after being outside ◆ Hypoallergenic bedding, pillows, cushions, soap, lotion, shampoo, detergent, etc.. - also fragrance-free Address co-occurring micronutrient deficiencies (B12, iron, Vit D, magnesium) Screen for autoimmune / inflammatory / metabolic disorders. Consider screening DEXA given the relationship between MCAD and osteoporosis. Mast cells cross-talk with autonomic nervous system - ANS regulation is key. ME/CFS pacing protocols can also be helpful. *Other treatments, benign and effective:* ● Quercetin start 250-500 mg, titrate to 500-1000 mg BID ● CoQ 10 start 100 mg BID, titrate to 200 mg BID ● Vitamin C sustained slow release start 500 mg daily ● Vitamin D - mast cell stabilizing and prostaglandin antagonistic effects ● Alpha lipoic acid 600 mg BID ● N-acetylcysteine (NAC) 600-900 mg BID ● Mitochondrial support - L carnitine (start 500 mg daily, can work up to 1000-2000 mg BID), D-ribose ● Omega-3 fatty acids Consider referral to MCAD-informed immunologist / hematologist - to discuss additional tx options such as Xolair, IVIG, hydroxyurea and others Treatment target of significantly reduced sx or resolution - for some patients certain meds/supplements may be life-long, although for many, after 2 years of stable improved state, meds can be systematically tapered / discontinued.	Additional cautionary notes: Quercetin often comes in combination with bromelain, which many MCAD patients have mast cell responses to. If this happens, look for quercetin-only formulation Prepare patients that cromolyn can worsen symptoms for 4-5 days (may need to increase antihistamines during that time). ● PO cromolyn best for GI symptoms (50-100 mg start daily 30 mins before meal; can titrate to 200 mg 4 times daily - must be separated from solid food before/after by 30 mins); if poorly tolerated, start with few drops in water daily ● Nebulized cromolyn for respiratory symptoms Many supplements are poorly absorbed; this can be improved by liposomal formulations

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Gastrointestinal disorders • IBS • Chronic functional constipation • Celiac disease • Food sensitivities & /intolerances *Further reading:* • Management of GI Symptoms in Food Hypersensitivity • Mast Cells & IBS • Microbiome & ADHD • GI & Autism mitochondria • Mast cells, IBS, & Food components	Many of these symptoms relate to dysautonomia and MCAD - manage as such. For MCAD, H1/H2 blockers, consider montelukast 10 mg daily (may require BID), consider oral cromolyn (50-100 mg start daily 30 mins before meal; can titrate to 200 mg 4 times daily - must be separated from solid food before/after by 30 mins); if poorly tolerated, start with few drops in water daily Even in the absence of celiac disease, consider trial of gluten-free diet to decrease zonulin and resultant intestinal permeability Food diary or http://whatthebleepcanieat.com to help identify triggers Refer to RD knowledgeable about MCAD Peppermint oil capsules (ie, Pepogest) PRN intestinal spasm H2 blocker has dual roles: reduce acid, synergism with H1 blocker re MCAD Sitting upright after eating to promote gastric motility and decrease reflux; these patients often have connective tissue disorders (floppier lower esophageal sphincter, more common hiatal hernias) Constipation - in addition to standard evaluation and management, consider that these patients often have co-occurring dysautonomia and connective tissue disorders that impacts constipation. • Refer to hypermobility-informed pelvic PT. • Optimize defecation posture(sitting upright at 90 degrees; some patients with known/suspected rectocele may also benefit from vaginal splinting) • May need postural supports during defecation • "MOO" method Treat SIBO empirically if testing not available (rifaximin often is covered by insurance for indication of IBS-D) Consider referral to MCAS-informed gastroenterologist *Anecdotal reports from patients of additional effective strategies (with benign side effect profile):* ginger, digestive bitters, pancreatic enzymes, DAO	• Consider role of chronic antacids (PPI/H2 blockers) in malabsorption • Caution: Neurodivergent people have high prevalence of eating disorders (current or past). Medically recommended restrictive diets can be problematic in this population. If patients report benefit from a particular diet (ie. low histamine diet), it may make sense to continue it for a period of time. Otherwise, in our practice we tend more toward education regarding trends of triggers as opposed to medical recommendations for specific elimination diets. • Negative celiac serologies does not rule out possible therapeutic benefit of gluten-free diet trial in this population • Peppermint oil capsules can be tremendously impactful for intestinal spasm; however, this smooth muscle relaxant can have a dramatic adverse impact on patients with connective tissue disorders - may worsen esophageal spasm and reflux.

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Pain syndromes • Fibromyalgia • Chronic Pain • Complex regional pain syndrome (CRPS) • Small Fiber Neuropathy (SFN) • Migraine *Further reading:* • LDN & chronic pain syndromes • LDN in chronic pain • LDN & CRPS • Role of melatonin in regulation of pain • Acupuncture & fibromyalgia	Need to thoughtfully consider potential conflicts of common chronic pain treatments in the presence of co-occurring ME/CFS, hypermobility, and/or dysautonomia). Even nonspecific exercise recommendations may not be a benign medical recommendation. Treat co-existing conditions (e.g. MCAD, dysautonomia, sleep disorders etc.) Trial magnesium supplement Correct concurrent micronutrient deficiency: i.e, Vitamin D, iron, B12 Low-dose Naltrexone ○ DIY compounding: Naltrexone 50mg diluted in 50mL H20- started at 1mg, work up to 4mg Education on pacing for both patients and their families / support circle Hypermobility-informed PT/OT and/or other allied health professionals for slow and safe movement guidance SFN In addition to common management strategies for neuropathic pain, consider • Melatonin 3-5mg/day • ALA (alpha-lipoic acid) 600 mg BID • B12, ALA, Carnitine • Treat underlying autoimmune etiology if present • Manage MCAD Migraine • In addition to standard management, identify and manage MCAD • In patients with hypermobility/EDS, high rates of co-occurring cervico-cranial instability (see EDS section above) • EDS patients also have higher rates of Chiari malformation • Consider vestibular rehabilitation if applicable	• Consider the connection to infections, allergies, PTSD and other triggers to autonomic nervous system dysregulation (which also impacts mast cell dysfunction) • Exercise recommendations with caution - may have coexisting ME/CFS, hypermobility • Muscle relaxants may worsen mechanical aspects of pain in the setting of hypermobility - best used in acute stage to assist with reducing subluxations; would avoid use at bedtime given risk of worsening underlying OSA • Some may have difficult recovery or acute reaction to manual therapy - they may need more gentle approaches and/or longer recovery • Lower doses of SSRIs often most effective • SNRIs may worsen some forms of dysautonomia • While “exercise” is an evidence-based treatment for fibromyalgia, the high prevalence of ME/CFS physiology in this population means that we cannot recommend anything that worsens post-exertional malaise (see below)

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Post-infectious chronic illness • Long COVID • ME/CFS ***Further reading:*** • Long Covid & melatonin • Long covid and its management • Long COVID & dysautonomia mgmt • MCAD & Long COVID • ME/CFS: What Primary Care Practitioners Need to Know • Dysautonomia & COVID • Long COVID & Dysautonomia Treatment • Antihistamines in acute COVID management • LDN in Long COVID • Mitochondrial dysfunction in ME/CFS	Long COVID introductory management: • Manage mast cell dysfunction / MCAD (see above) beginning with antihistamines and trigger avoidance (may be helpful to start during acute COVID). • Melatonin • Vitamin D • Manage components of Long COVID listed separately in this guide (i.e., POTS/dysautonomia, SFN) • ME/CFS Pacing protocol (physical and cognitive) - see NHS resource – may need to take time off from work or school or reduce hours; • Goal is systemic anti-inflammation: Treat MCAD if present; treat any coexisting infections (SIBO, candida, skin infections, periodontal disease), manage other systemic inflammatory conditions; consider anti-inflammatory diet • Reduce sympathetic nervous system activation • LDN • Essential to prevent COVID re-Infection - Long COVID symptoms worsen with subsequent COVID infection. • Mitochondrial support - see MCAD section • NAC • Micronutrient support - including B vitamins, acetyl L-carnitine, and those listed above • Consider liposomal luteolin Preventing Long COVID • Prevent acute COVID - particularly if prior infection, important to note that risk of Long COVID increases with subsequent infections • Treat acute COVID - antihistamines (both H1 blocker and H2 blocker), melatonin, quercetin, Vitamin C, NAC. consider Paxlovid or metformin • Melatonin deficiency identified as a mechanism of LC in autistic adults - start melatonin 1-3mg in acute COVID • ME/CFS Pacing protocol - consider thinking about acute COVID similarly to the management of concussion • This is a helpful literature review	Do NOT recommend graded exercise therapy, cognitive-behavioral therapy, or any treatment aimed on "pushing through" post-exertional malaise – this may WORSEN the clinical trajectory Significant co-occurrence of Long COVID and neurodivergent burnout, both of which increase risk of suicidality. Suicide is already one of the leading causes of death for autistic people. **It is critical that patients receive the message that Long COVID is treatable – not in the future, not with more research…. today.** Given higher risk of thromboembolism, maintain higher index of suspicion for such even in young patients This vulnerable patient population needs clinicians to advocate for them to be able to safely participate in their communities without getting acute COVID (again, or for the first time). Consider impact of post-exertional malaise in ANYTHING we are asking these patients to do - exercise, testing, even attending medical appointments Given co-occurrence with MTHFR methylation deficits, B complex supplements should be those with methylfolate

Condition	Treatment / Supports (in addition to standard primary care management)	Cautionary notes & Contraindications
Reproductive • Endometriosis • PCOS • PMDD	In addition to standard management, consider treating empirically for MCAD - can increase regimen during symptom flares (for example, doubling H1/H2 blocker doses during the week of menses or other hormonal shifts / cyclical triggers). Mast cells are responsive to shifts in estrogen, thus explaining flares in symptoms in response to endogenous shifts in estrogen (perimenstrual / perimenopausal triggers). • Check and treat iron/ferritin/anemia if dysmenorrhea • Menstrual suppression if needed for menstrual irregularity, dysmenorrhea, or significant MCAD/dysregulation surrounding menstruation • Increased risk of insulin resistance with PCOS even with normal body weight- mast cell management may improve insulin resistance • Address ANS dysregulation and resultant impact on cortisol patterns	Given that trans and gender non-conforming patients are more likely to be autistic, it is important to monitor for mast cell flares while starting / titrating gender-affirming hormone treatment. These patients may benefit from increasing MCAD medications during this time. While Ozempic can be hugely helpful, may increase gastroparesis in this population with co-occurring dysautonomia
Dental • Temporomandibular dysfunction (TMD) • Ankyloglossia • Periodontal disease (related to collagen abnormality and immune dysfunction in this population) *Further reading:* • Management of periodontal disease • TMD Management	Dentists and PT/OT/SLP with specific expertise in hypermobility Optimize MCAD. Also consider allergen-free toothpaste - this may be an MCAD trigger Soft toothbrush Water after and during meals to rinse out food Consider chlorhexidine mouthwash to decrease bacterial load, though some patients do have an mast cell response to this Consider Vitamin C and/or Vitamin D supplementation TMD - additional considerations: • Evaluate for OSA with TMD/teeth grinding • Consider role of TMD in migraines/cervical tension	Caution releasing oral tethers prior to addressing potential underlying hypermobility, low tone, oral myofunctional skills Caution with muscle relaxants for TMD: may worsen OSA Orthodontics management (braces, palate expanders, etc) often only temporary-hypermobility causing symptom relapse. Also caution re metallic hardware given high rates MCAD metal sensitivity) Night guards for grinding don't address underlying problem – also need to eval for OSA, cranio-cervical instability, etc.

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