

The International Consortium on Ehlers-Danlos Syndromes & Related Disorders

In Association with The Ehlers-Danlos Society

Evaluation and Management of Fatigue in Patients with Ehlers-Danlos Syndrome

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- I have no financial conflicts of interest to disclose
- I will discuss "Off-label" uses of some medications



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 Chronic fatigue in Ehlers–Danlos syndrome–
 Hypermobile type
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Chronic Fatigue Evaluation

- Thorough history and physical examination: Fatigue is a common symptom in many systemic illnesses.
- History should include exacerbating and alleviating factors, sleep disturbance and stressors, and impact on wellbeing.
- Include assessment of psychological wellbeing both as a cause and an impact.

Chronic Fatigue Treatment

General key principles:

- To facilitate effective management the clinician needs to establish a collaborative relationship with the patient and their caregivers.
- Engagement with the family is particularly important for children and young people, and for people with severe fatigue.
- The patient and their clinician should share decision making both in identifying the causes of, recognizing the impact of, and developing a treatment plan for fatigue.

Chronic Fatigue Treatment

General key principles:

- People with severe fatigue may need support from a multidisciplinary team e.g., nursing, occupational therapy, dietetics, psychology, physiotherapy, and pain management.
- This should be coordinated by a named healthcare professional, and usually their general practitioner / general physician.

Chronic Fatigue Treatment

General key principles:

- An individualized, patient-centered program should be offered.
- Objectives: gradually extend and sustain the person's physical, emotional and cognitive capacity.
- Treatment is based on addressing the underlying issues.
- Disruption of education or employment is generally detrimental to health and wellbeing. The ability to continue in these should be addressed early.

Many, Many Factors Contribute to Fatigue in EDS

- The Big Three: Pain, Poor Sleep, Depression
- Autonomic Nervous System Dysfunction
- Metabolic Factors, e.g. Dehydration, Nutrient deficiency
- Inadequate Rest
- Cognitive Tasks
- Emotional Stress
- Everyday Life



Address Everything Together

- To break the cycle, you need to address all contributing factors simultaneously, because...
- As long as you're in pain, your sleep, your depression, and your fatigue will never get completely better.
- As long as you're depressed, your pain, sleep, and fatigue will not improve very much.
- There is no "magic formula."

Everybody's Different

- No two patients have identical symptoms.
- Response to symptoms, medications, etc. vary with:
 - Psychological factors
 - Basic personality, e.g. optimist/pessimist
 - Life (e.g. work, family, financial) situation
 - Support system
 - Physiological factors
 - Pre-illness state of health
 - Other medical conditions
 - Pharmacogenetics, other genetic factors

Every Patient Requires a Comprehensive, Individualized Treatment Plan

Different Types of Pain Require Different Treatments

Accurate diagnosis is the first step

• Pain

- Inflammatory
 - (NSAID's, e.g. ibuprofen, Celecoxib, meloxicam
 - Steroids, e.g. prednisone
- Mechanical
 - Muscle relaxants, e.g. cyclobenzaprine, tizanidine
 - Physical measures, e.g. heat, physical therapy, massage, dry needling
- Neuropathic
 - Gabapentin, pregabalin, duloxetine, milnacipran

Pain—Don't Underestimate It

- •It's not that bad
- •I' m used to it
- •I' ve learned to live with it
- •I don't want to take pain medication

Are all things I regularly hear from patients in pain, but these *are not helpful approaches to managing chronic pain*

- "Background" pain
- Pain is masked by adrenaline

Different Types of Depression Require Different Treatments

- Depression
 - Serotonergic Symptoms (SSRI's, e.g. escitalopram)
 - Noradrenergic Symptoms (SNRI's, e.g. milnacipran, duloxetine)
 - Dopaminergic Symptoms (bupropion)
 - Symptoms that Suggest a Bipolar Disorder (mood stabilizers)

Norepinephrine Serotonin Anxiety Pain Impulse Obsessions Alertness Irritability & Compulsions Concentration Memory Energy Mood **Cognitive Function** Appetite Attention Sex Aggre ssion Pleasure Reward Motivation/Drive Dopamine Source: Deplin[™] pamphlet

Depression—Don't Underestimate It

- •It's not that bad
- •I' m used to it
- •I' ve learned to live with it
- •I don't need counseling
- •I don't want to take antidepressants

Are all things I regularly hear from patients who are depressed, but like pain, these **are not helpful approaches to managing depression**

Remember:

- One doesn't have to be sad to be depressed.
- Neurotransmitter deficiency can be significant even in the absence of clinical depression
- Don't overlook non-pharmacologic measures that help depression, e.g. counseling, exercise, relaxation/stress management techniques, etc.

Different Types of Sleep Problems Require Different Treatments

- Difficulty getting to sleep
 - Anxiety
 - Pain
 - Something else, e.g. restless legs
 - "Environmental" factors—uncomfortable mattress, noise, light, restless or noisy bed partner
- Trouble staying asleep
 - Pain, sleep apnea, snoring, vivid dreams
- Hard time getting back to sleep
 - Any of the above

Don't Underestimate How Bad Sleep Is

- •It's not that bad
- •I'm used to it
- •I've learned to live with it
- •I don't want to take sleep medication

Are things that patients who don't sleep well will say, but again, these *are not helpful approaches to managing sleep disorders*

Sleep "Misperception"

- Perhaps even more than pain and depression, sleep is often misperceived:
- "I'm a great sleeper"
- Up to 90% of patients with sleep apnea don't know they have it
- Many patients with periodic limb movements also are unaware that they're moving at night
- Frequent arousals and lack of deep sleep, common causes of non-restorative sleep in EDS, often don't cause any symptoms except fatigue on waking

Sleep Studies

- Sleep studies are usually very helpful, *if carefully interpreted*
- Home sleep monitoring, if available, can also be very helpful, though currently available monitors have significant limitations
- Home heart rate monitors can be helpful in estimating sleep disruption

Non-Restorative Sleep in EDS

- Frequent arousals and awakenings
- Little or no deep sleep







Treatment of Sleep Disorders

- Don't overlook the basics:
 - Good sleep hygiene
 - Comfortable mattress
 - Dark and quiet
 - Elevate head of bed (if lightheaded during the day)
 - Treat sleep apnea, limb movements only if significant

Treatment of Sleep Disorders: Medication

• Complex medication "regimen" is often required:

- Multiple medications with complementary effects, e.g. one medication for pain, one to reduce arousals, one to increase deep sleep
- Finding the right combination can be a frustrating trial and error process
- Home sleep monitor might be helpful

Treatment of Sleep Disorders: Medication

- Block extra adrenaline (beta and alpha blockers, clonidine and guanfacine)
- Offset extra adrenaline (benzodiazepines, SSRI's)
- Reduce pain (analgesics, muscle relaxants, Neurontin[™], Lyrica[™])
- Increase deep sleep (trazodone, amitryptiline, mirtazepine)
- Use "Sleeping pills" sparingly

The Autonomic Nervous System

- Autonomic nervous system regulates all functions that occur automatically, e.g. circulation, breathing, digestion, body temperature etc.
- Maintains balance, "steady state," homeostasis
- Sympathetic—"fight or flight," the accelerator
- Parasympathetic—"rest and digest," the brake

Autonomic Dysfunction in EDS

 Characterized by fluctuations, failure to maintain stability, and overresponse to minor perturbations, stresses, or stimuli

Sympathetic and Parasympathetic Activity with Autonomic Maneuvers



A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand

ANS Dysfunction is an Energy "Drain"

- Autonomic fluctuations, overresponding to minor stresses wastes the energy you're trying to conserve
- Medications that reduce or offset overresponse can both conserve energy and reduce symptoms:
 - Beta blockers
 - Clonidine/guanfacine
 - SSRI's, usually at low doses
 - Benzodiazepines, e.g. diazepam, lorazepam, clonazepam

Different Causes of Fatigue Require Different Treatments

• Much of the Fatigue in EDS comes from:

- Poor Sleep
- Chronic Pain
- Depression
- Autonomic Dysfunction

But that doesn't mean that these are the *only* causes of fatigue. Common metabolic factors need to be looked for, too.

Common Metabolic Factors in Fatigue in EDS

- Anemia, hypothyroidism, and other "common" problems
- Micronutrient deficiencies, especially Vitamin D, Vitamin B12, and Magnesium
- Hormone deficiencies, especially cortisol, DHEA/testosterone
- •Salt/fluid imbalance, usually inadequate salt and/or excessive water intake
- Mast cell dysfunction

Assessing Salt-Fluid Balance

- Serum Osmolality
 - Normal ranges usually 280-300
 - Most people with orthostatic intolerance are around 280
- Urine Osmolality
 - Normal ranges usually 300-1000
 - Many people with orthostatic intolerance are below 300, often way below!

Treating Salt-Fluid Imbalance

- Most People with Orthostatic Intolerance, told to drink lots of water and eat lots of salt, are getting too much water and not enough salt!
- Electrolyte drinks are the best "solution," but be careful, because many have lots of sugar
- Limit plain water to less than half of daily fluid intake
- Forget the conventional wisdom that salt is bad
- Most people don't need >2-3 liters of fluid a day
- Compression hose can be very helpful, and not as unsightly as the ones your grandma wore

Mast Cell Dysfunction

- Now clearly associated with EDS
- Typically causes respiratory, skin, and/or digestive problems, but can affect virtually every organ system
- Mast cell overactivity also can aggravate autonomic problems, fatigue, sleep, and pain
- Dietary measures (i.e. "low-histamine diet") and pharmacological measures (e.g. antihistamines, cromolyn, montelukast) are usually both necessary to control symptoms

Stimulants

- Traditional stimulants, like those used to treat ADD, can be effective in small doses to raise heart rate and blood pressure in people who are often lightheaded,
- BUT They must not be used to treat fatigue, i.e. to enable people to keep going when they are really exhausted and should be resting. This tends to cause a "crash" when the medication wears off, and over time just worsens fatigue.
- Modafinil/armodafinil often improve alertness, focus, productivity, without being physically stimulating

So How Do You Reduce Fatigue in Patients with EDS?

By identifying as many contributing factors as we can, and addressing as many as possible in a comprehensive treatment program





And This Is How Fatigue in EDS Patients Gets Better!

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