Evaluation and Management of Fatigue

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I will discuss “off-label” uses of some medications.
I have no financial conflicts of interest to disclose.
Evaluation of Fatigue

• Thorough history, physical and laboratory examination, because fatigue is a common symptom of many illnesses.

• More specific testing, e.g. of sleep, nutrition, and autonomic dysfunction, can also be helpful.

• Thorough evaluation is critical because treatment will be based primarily on the results of the evaluation
Many Factors Contribute to Fatigue in EDS

The Big Three:  Pain, Poor Sleep, Depression
Autonomic Nervous System Dysfunction
Metabolic Factors
Inadequate Rest
Cognitive Tasks
Emotional Stresses
Everyday Life
Fatigue

Depression

Pain

Poor Sleep
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,” because everyone’s different.
“Ask your doctor if taking a pill to solve all your problems is right for you.”
Pain

How does pain cause fatigue?
• Pain saps your energy
• Pain limits your activity
• Pain disrupts your sleep
• Pain causes depression
• A variety of other mechanisms
Cortisol

Cortisol is produced in response to stress, including pain. Common signs and symptoms of too much cortisol include:

• weight gain, mostly around the abdomen, upper back, and face
• Acne, facial flushing, headache
• thinning skin, easy bruising, slowed healing
• muscle weakness
• **severe fatigue**
• irritability
• Trouble concentrating
• Increased blood pressure
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 Pain Require Different Treatments

- **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
Non-Pharmacological Treatments for Pain

- Physical Therapy
- Exercise
- Acupuncture
- Devices, e.g. TENS.
Medications for Pain

- Acetaminophen
- NSAID’s
- Antidepressant analgesics (e.g. duloxetine)
- Neuropathic analgesics (e.g. gabapentin)
- “Adjunctive” medications, e.g. muscle relaxants
- Topical/local medications, e.g. creams, gels, patches
- Opioids
- Cannabinoids (in some U.S. states)
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
Of course I’m depressed, wouldn’t you be?
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, spending time with hobbies or pets, etc.
Different Types of Depression Respond to Different Pharmacological Treatments

- 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)
"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."
Different Types of Sleep Problems Require Different Treatments

Difficulty getting to sleep
   Anxiety, Pain, Restless legs, “hyperarousal”
   Environmental factors—uncomfortable mattress, noise, light, restless or noisy bed partner

Trouble staying asleep or getting back to sleep
   Pain, sleep apnea, snoring, vivid dreams

Just waking up unrefreshed
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’ve never been a good sleeper
I don’t want to take sleep medication
Are things that patients who don’t sleep well 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”

Many patients with sleep apnea and periodic limb movements don’t know they have them.

Frequent arousals and/or 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, but only if carefully interpreted.

Home sleep monitoring can also be very helpful.

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

Normal Sleep

Non-Restorative Sleep
Treatment of Sleep Disorders

Don’t overlook the basics:
Good sleep hygiene
Comfortable mattress
Dark and quiet
Treat sleep apnea, limb movements only if significant
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 can be helpful
Treatment of Sleep Disorders: Medication

Block extra adrenaline (beta and alpha blockers, clonidine and guanfacine)
Block histamine (diphenhydramine, hydroxyzine)
Offset extra adrenaline (benzodiazepines)
Reduce pain (analgesics, muscle relaxants, gabapentin, pregabalin)
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:
Failure to maintain stability
Excessive fluctuations
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 Aggravates Fatigue

Autonomic fluctuations, overresponding to minor stresses wastes the energy you’re trying to conserve
Autonomic dysfunction impairs sleep quality
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, e.g. DHEA/testosterone
- Salt/fluid imbalance, usually inadequate salt and/or excessive water intake
- Mast cell dysfunction
Micronutrient Deficiencies: Vitamin D

Normal Vitamin D level is 30-100
Many people have levels in the teens or low 20’s
To increase your level from 20 to 40 requires roughly ONE MILLION units of Vitamin D
I recommend a 50,000 unit D3 supplement (Bio-Tech Labs) weekly until deficiency is corrected, then less often
Micronutrient Deficiencies: Vitamin B12

“Normal” B12 levels are 200-1100, but Almost everyone below 300 is clinically deficient. B12 deficiency is most often caused not by inadequate intake but rather by impaired absorption. If deficient, I recommend weekly subcutaneous shots for several months, followed by less frequent maintenance doses.
Micronutrient Deficiencies: Magnesium

Only 1-2% of magnesium is in the bloodstream. Red Blood Cell magnesium levels are more sensitive at detecting deficiency.

Trial of extra magnesium is often worthwhile, especially for reducing muscle pain and spasm.

Oral magnesium is not well absorbed, and often causes diarrhea, but magnesium is well absorbed through the skin, so consider oils, Epsom salts.

I often liken correcting magnesium deficiency to filling a bucket with an eye dropper!
Testosterone Deficiency

Many EDS patients have trouble building muscle, even with good diet and exercise regimens. I have found that a significant percentage of EDS patients, especially thin young women, have abnormally low testosterone levels. Treatment with small amounts of testosterone, usually topically, or with oral DHEA, which the body can convert into testosterone, is often helpful, not just for building muscle but for mood and fatigue and libido as well.
Salt-Fluid Imbalance

Adequate hydration is important for reducing lightheadedness, autonomic instability, and fatigue. Most people who report feeling lightheaded on standing are told to eat lots of salt and drink lots of water, but surprisingly I have found that almost without exception these people are getting too much water and not enough salt.

If no matter how much water you drink you’re still thirsty, then paradoxically you’re probably drinking too much water.

Check random urine sodium. If low, you’re getting too much plain water and/or not enough salt.
Treating Salt-Fluid Imbalance

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 for you
Most people don’t need >2 liters of fluid a day
Most people don’t need fludrocortisone
Compression hose can be very helpful
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 chronically 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 you can, and addressing as many as possible in a comprehensive treatment program.
Reverse the Vicious Cycle

- Improved Mood
- More Energy
- Better Sleep
- Less Pain
And That Is How Fatigue in EDS Patients Gets Better!
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