

# Breaking the Cycle of Chronic Pain, Poor Sleep, Depression, and Fatigue in Patients with EDS

Alan G. Pocinki, M.D.  
Metro DC EDS Support Group  
May 18, 2019

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

Depression

Fatigue

Pain

Poor  
Sleep

Depression

Pain

Fatigue

Poor  
Sleep

# Myopain 2013

- “Every patient with chronic widespread pain requires evaluation of sleep, since poor sleep and depression are independently associated with pain.”
  - Dr. Phillip Mease, University of Washington

# Address Everything Together

- To break the cycle, you need to address all contributing factors simultaneously, e.g.
- 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
    - Who you are
    - Your life situation
    - Your support system
  - Physiological factors
    - Pre-illness state of health
    - Other medical conditions
    - Pharmacogenetics, other genetic factors

**“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.”**

**Sir William Osler**





Every Patient Requires a  
Comprehensive,  
Individualized Treatment Plan



*"Ask your doctor if taking a pill to solve all your problems is right for you."*

# 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



*"Does it hurt when I do this?"*

# A Pain-o-Meter?

- A recent study (*Molecular Psychiatry* 24:501-522, 2019) reported the discovery of biomarkers in the blood which the lead author, Dr. Alexander Niculescu, claims can help objectively determine how severe a patient's pain is. This approach could one day lead to:
- Validation of a patient's reports of pain
- More widespread recognition that not only do different people have different types and severities of pain, but their bodies respond differently to it
- Tailoring of treatment programs to individuals, with different biomarker profiles used to help predict which types or amounts of medication might be most likely to be effective for specific patients.

# 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

# Different Types of Pain Require Different Treatments

- Accurate diagnosis is the first step
- Pain
  - Muscle/joint
    - Inflammatory, Mechanical, Neuropathic
  - Visceral
    - Inflammatory, Mechanical, Neuropathic, Ischemic
  - Headache
    - Inflammatory, Mechanical, Neuropathic, Vascular, CSF-related

# 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
- Heat/Cold
- 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

***Are not helpful approaches to managing depression***


# Remember:

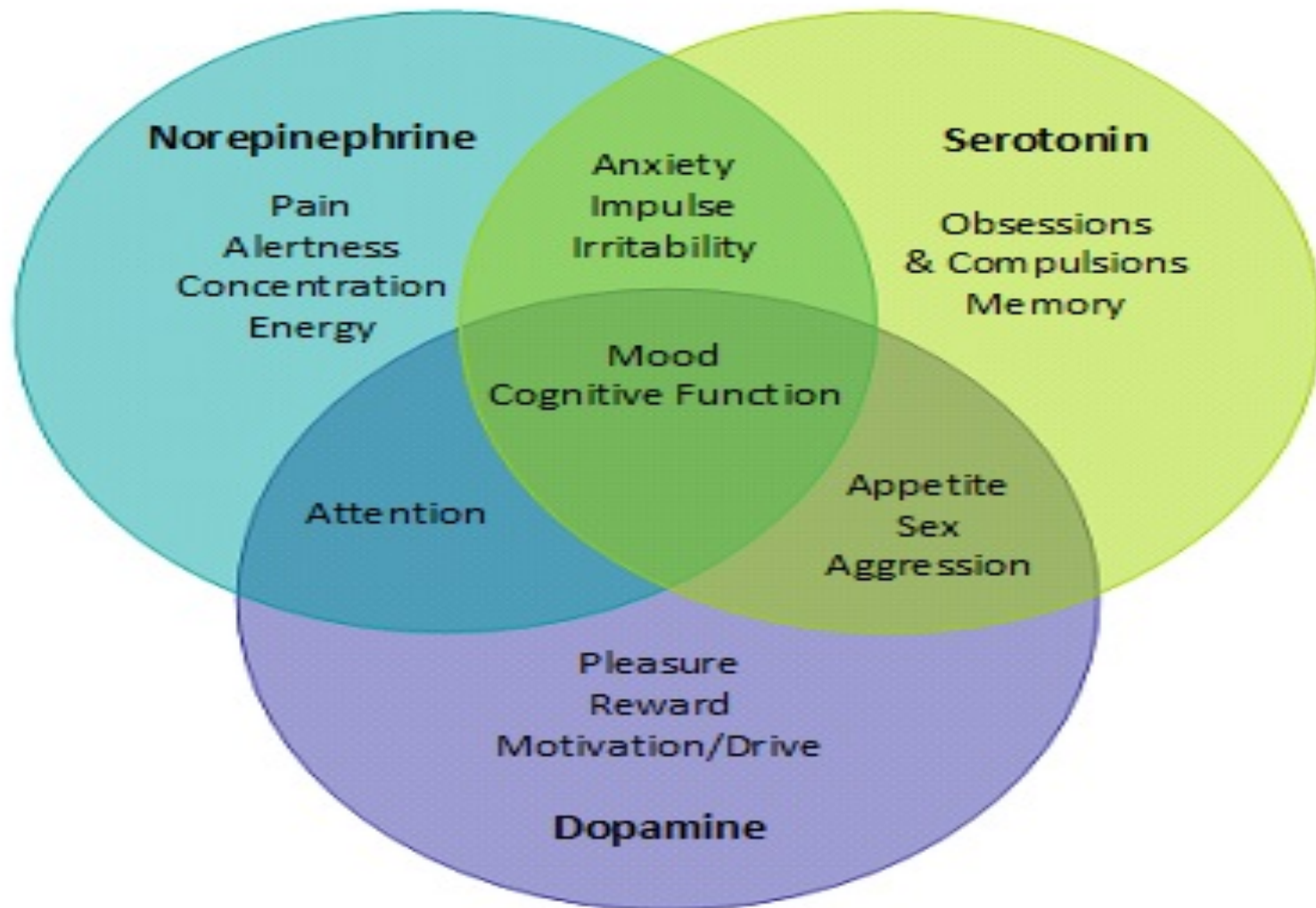
- One doesn't have to be sad to be depressed.
- *Neurotransmitter deficiency can be significant even in the absence of clinical depression*
- Don't overlook non-pharmacologic measures that help depression, e.g. counseling, exercise, relaxation/stress management techniques, spending time with hobbies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

Rx & TLC



JONNY  
HAWKINS

- 
- If non-pharmacologic measures aren't sufficient to treat depression, then the choice of antidepressant medication should be based on the specific depression symptoms



•

Source: Deplin™ pamphlet

# Different Symptoms of Depression Tend to Respond Better 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."*

# Don't Underestimate How Bad Your 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 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 lack of deep sleep, common causes of non-restorative sleep in EDS, often don’t cause any symptoms except not feeling rested on waking

# Different Types of Sleep Problems Require Different Treatments

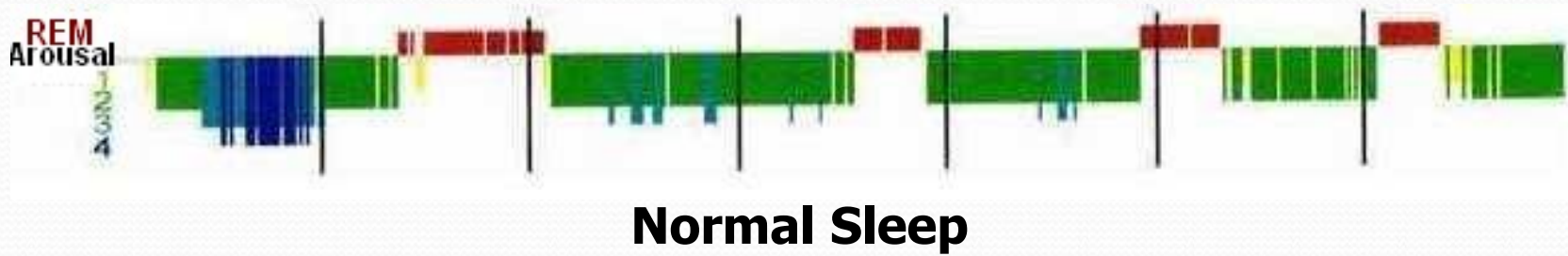
- Difficulty getting to sleep
  - Anxiety, Pain, Restless legs, “hyperarousal”
  - Environmental factors—uncomfortable mattress, noise, light, restless or noisy bed partner
- Trouble staying asleep or getting back to sleep
  - Pain, sleep apnea, snoring, vivid dreams
- Just waking up unrefreshed

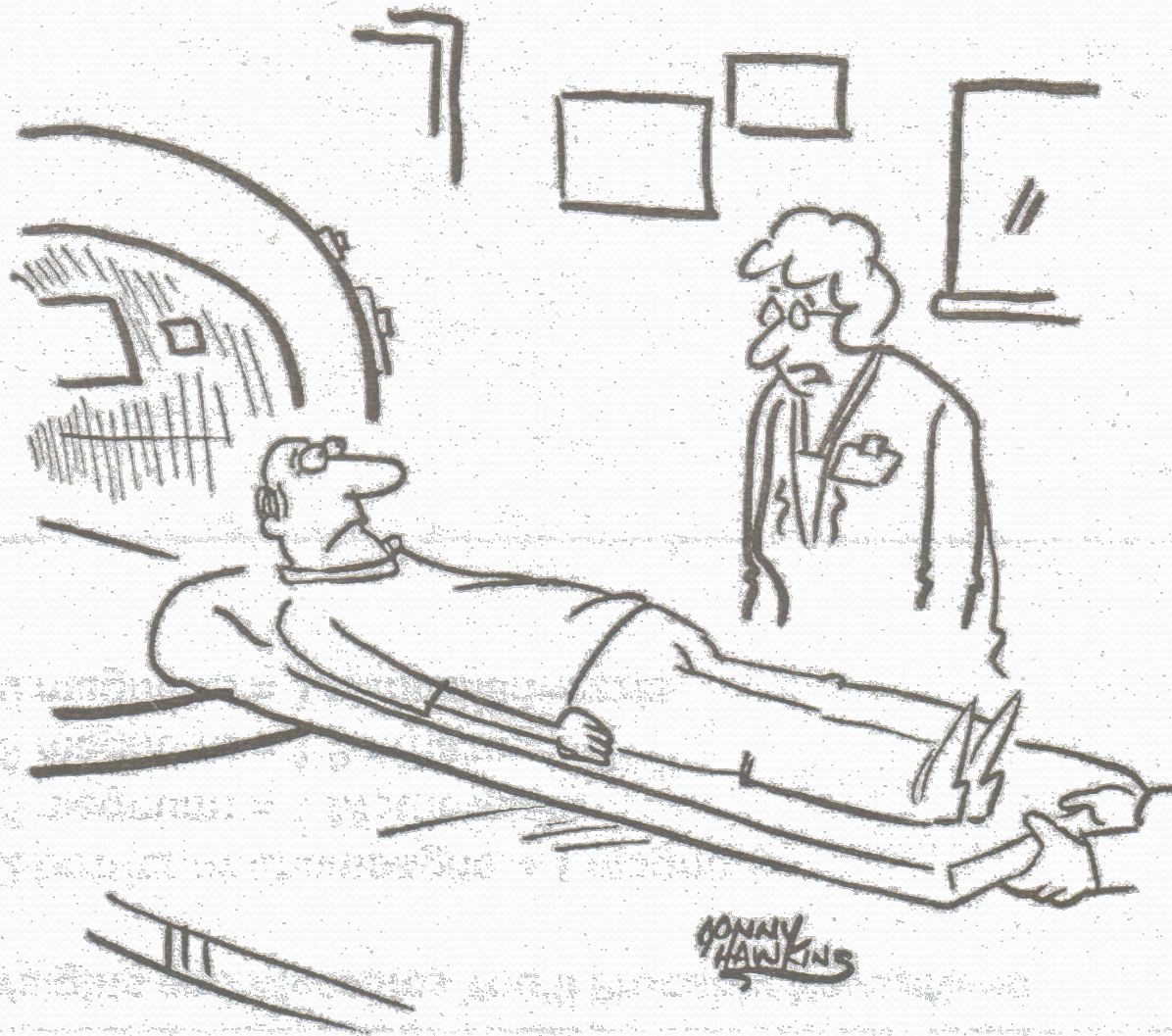
# Sleep Studies

- Sleep studies are usually very helpful, *if carefully interpreted*
- Home sleep monitoring, if available, can also be very helpful, though currently available monitors have 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

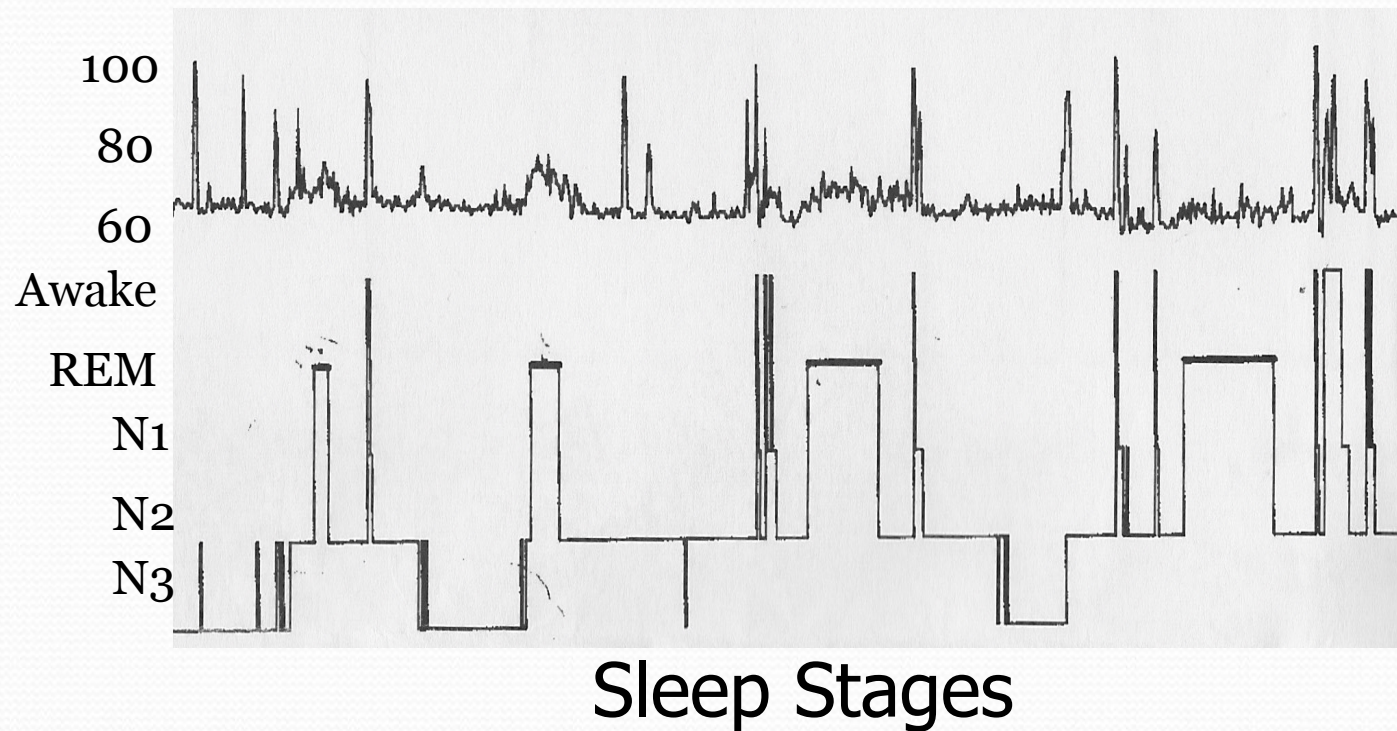




"The MRI reveals that your head is riddled with conventional wisdom."

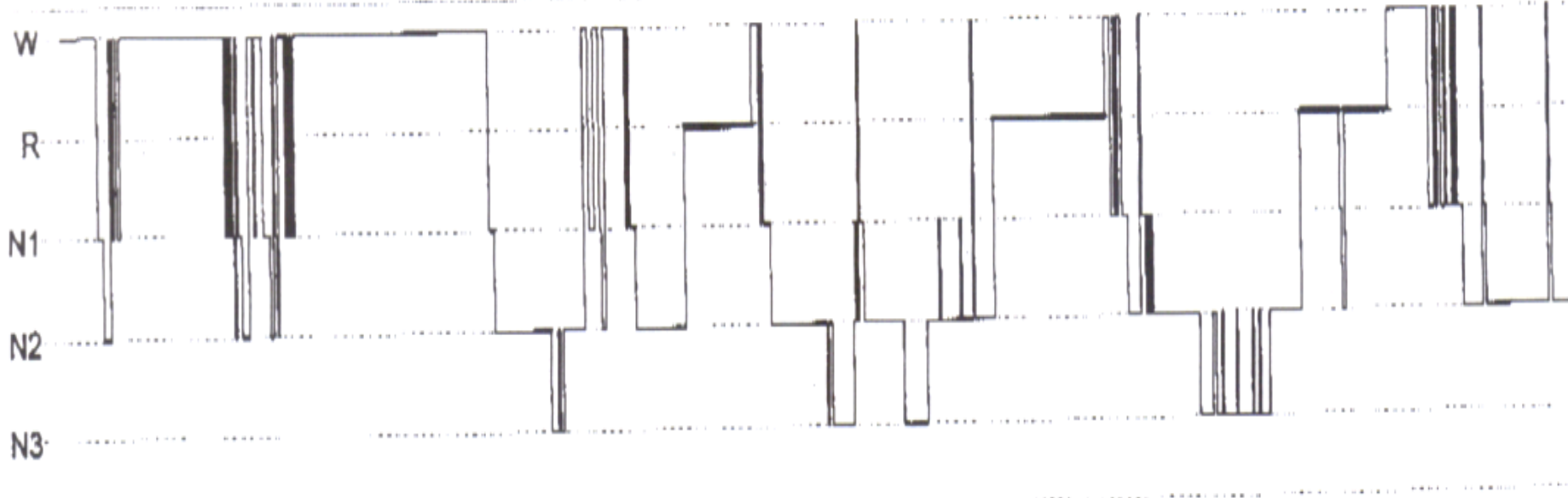
# Heart Rate Fluctuations Associated with Sleep Disruptions

## Heart Rate



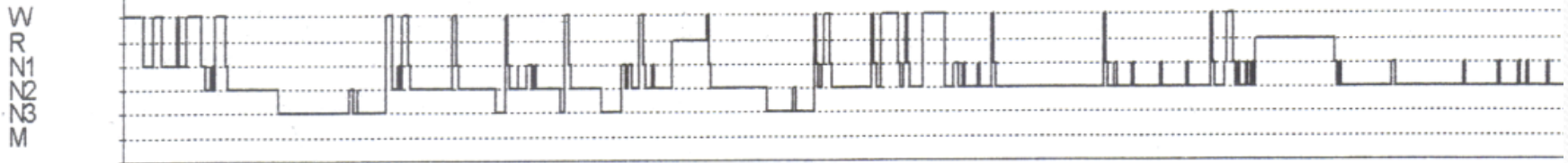


# Sleep Stages

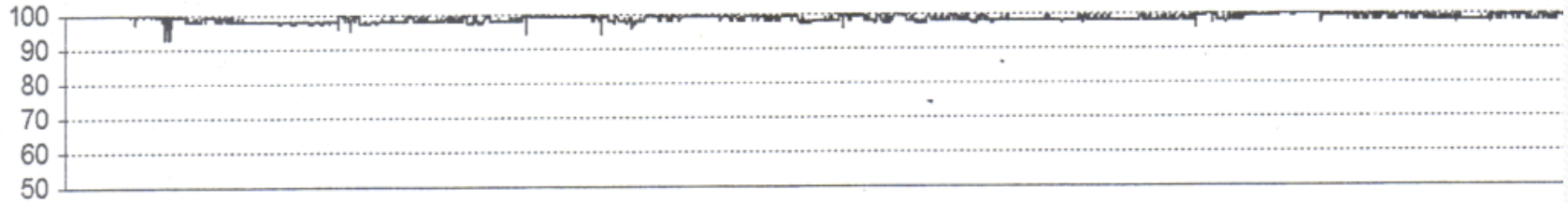


W=Awake, R=REM, N1 and N2=Shallow sleep, N3=Deep sleep

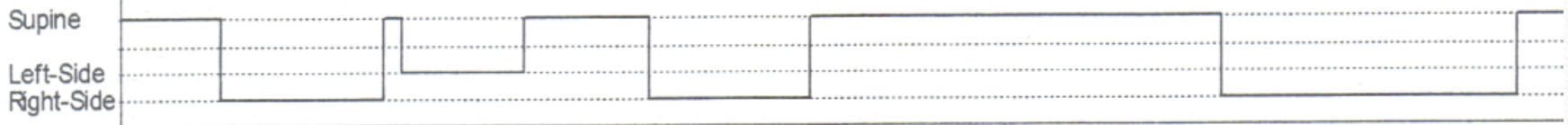
### Hypnogram



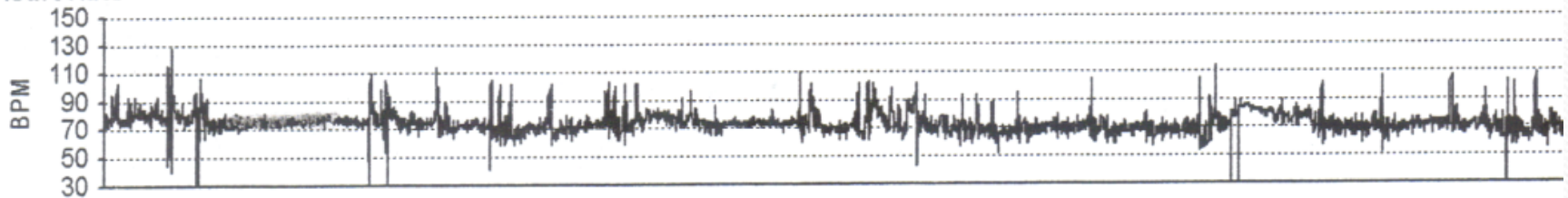
### SaO2%



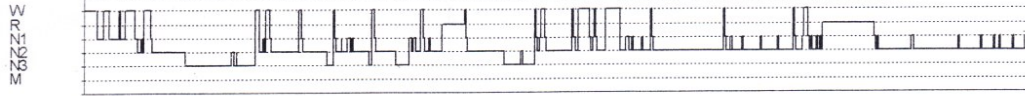
### Body-Position



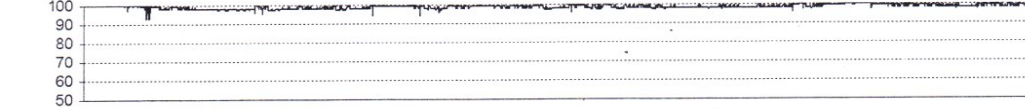
### Heart Rate



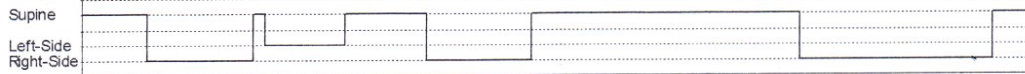
Hypnogram



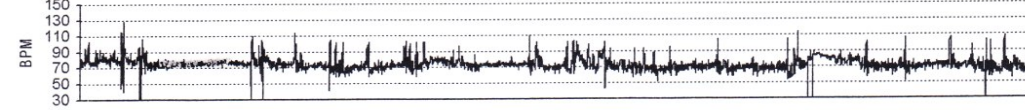
SaO2%



Body-Position



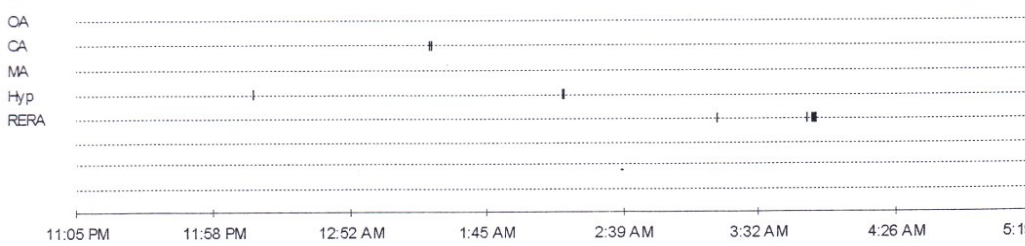
Heart Rate



CPAP/BiPAP Titration



Events



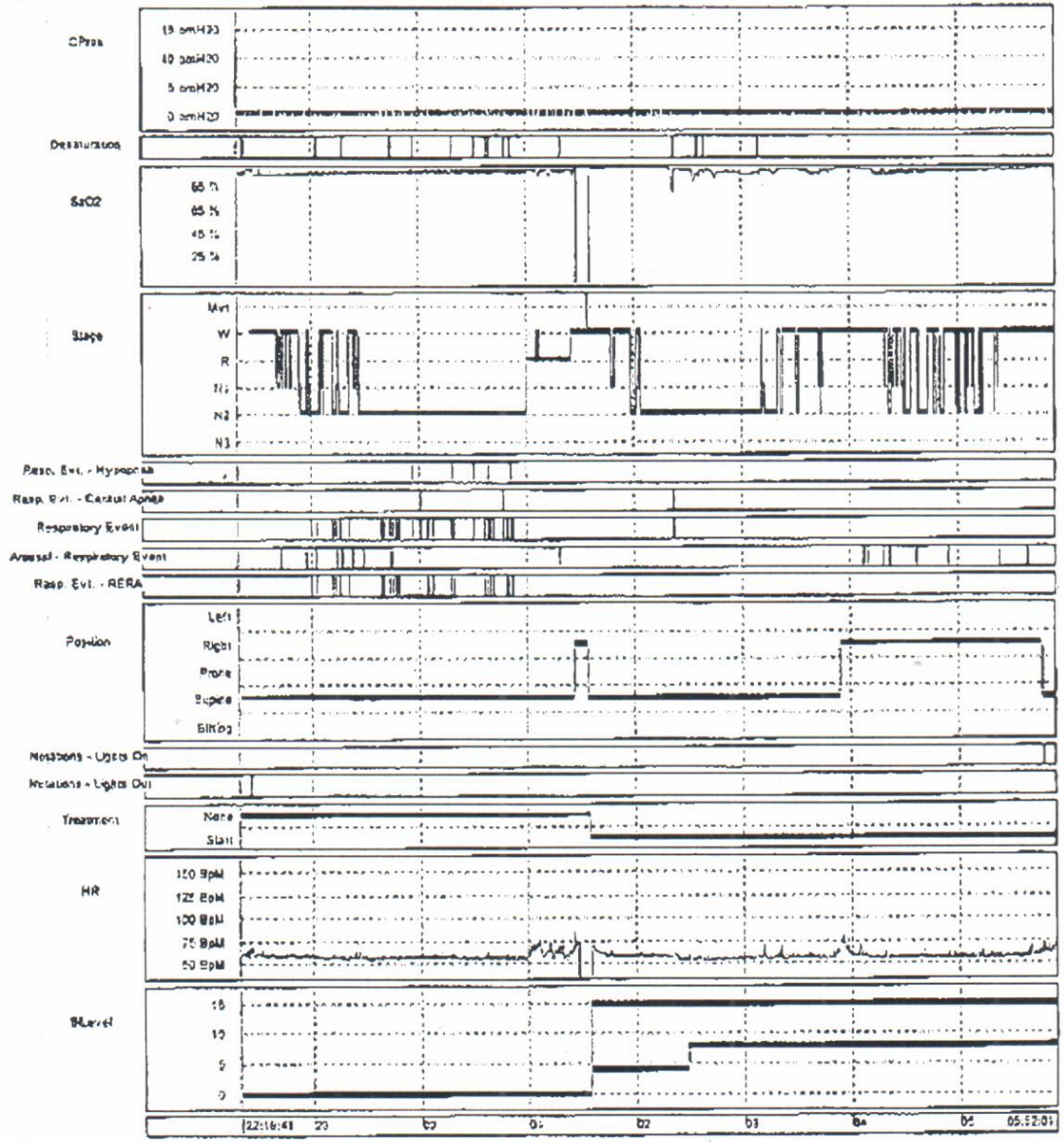
11:05 PM 11:58 PM 12:52 AM 1:45 AM 2:39 AM 3:32 AM 4:26 AM 5:19 AM

# Today

Fat Burn Cardio Peak



ograms



# 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**

# 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 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 stability, “homeostasis”
- Sympathetic—“fight or flight,” the accelerator
- Parasympathetic—“rest and digest,” the brake

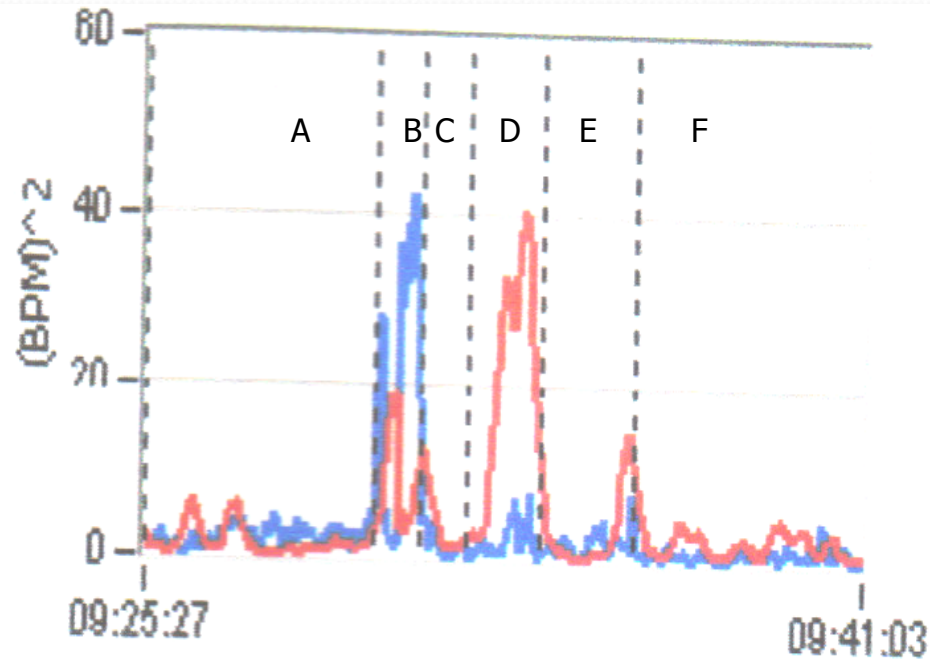
# Autonomic Dysfunction in EDS

- Autonomic dysfunction can both cause and be caused by pain, fatigue, and poor sleep.
- Characterized by fluctuations; failure to maintain stability; overresponse to minor perturbations, stresses, or stimuli

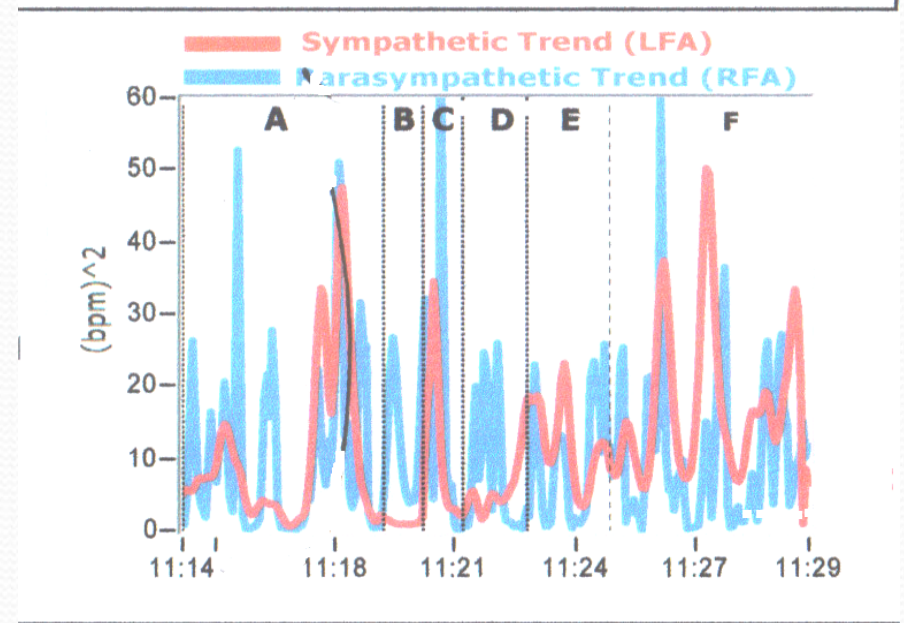
# Autonomic Dysfunction in EDS

- Concept of autonomic reserve, “depletion”
- ***Central paradox: the lower the reserves, the more exaggerated the stress response***
- The body “overresponds” to minor stresses
- The overresponse often triggers an overcorrection, then an overresponse...

# Sympathetic and Parasympathetic Activity with Autonomic Maneuvers

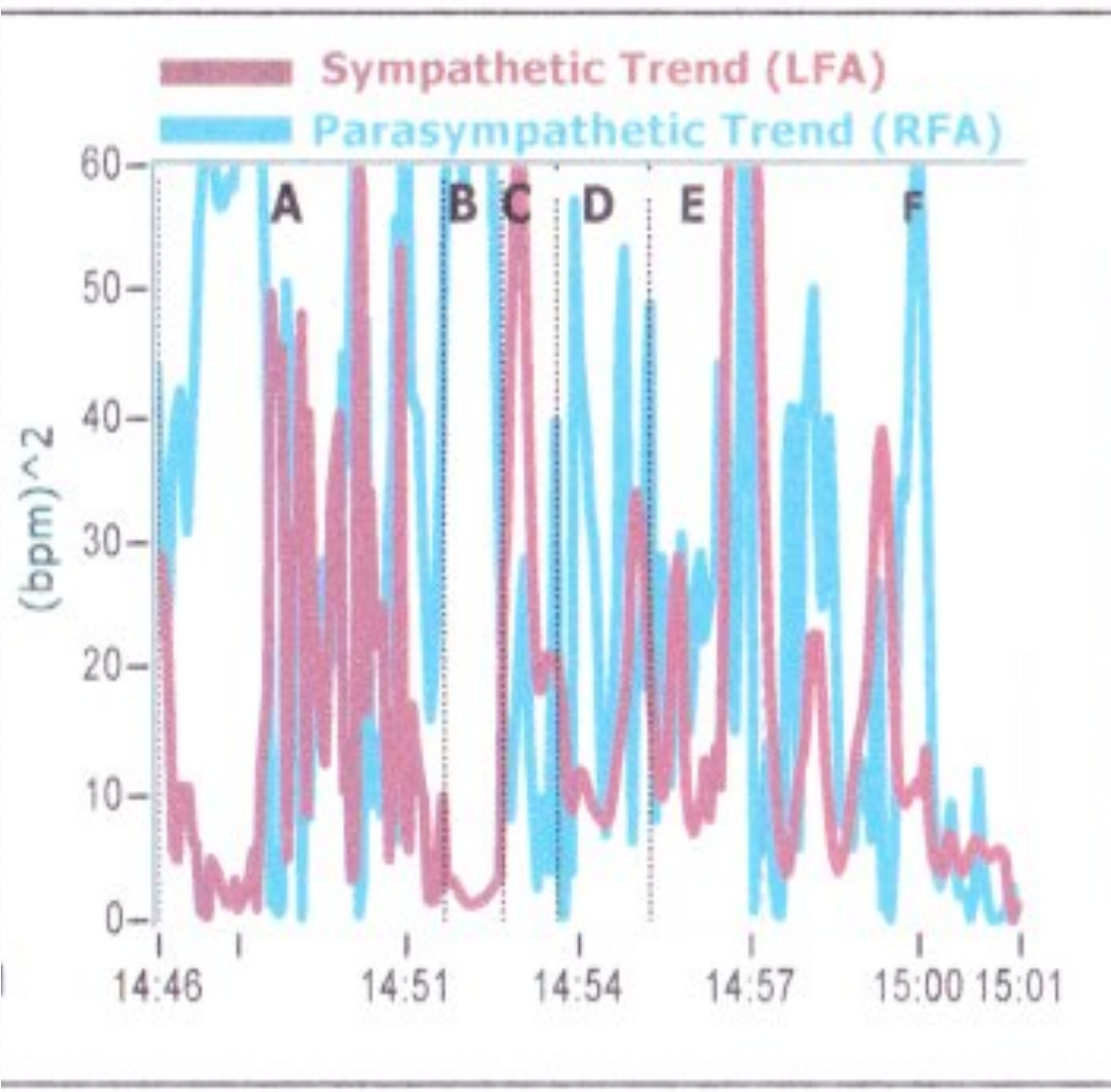


Normal



EDS with Dysautonomia

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

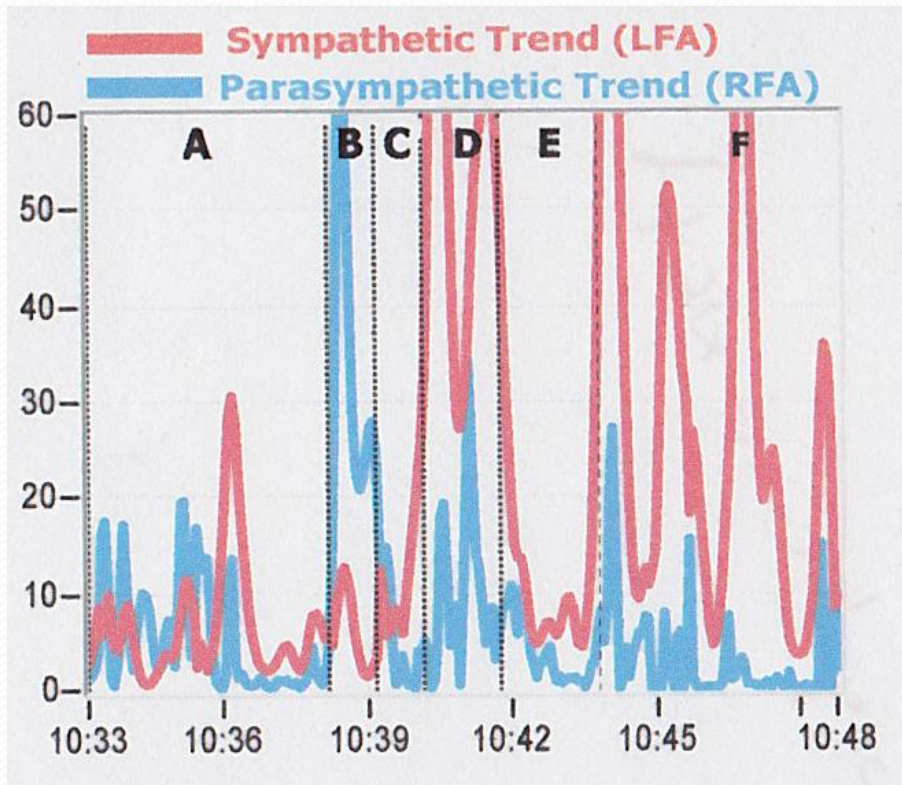


# Symptoms of ANS Dysfunction

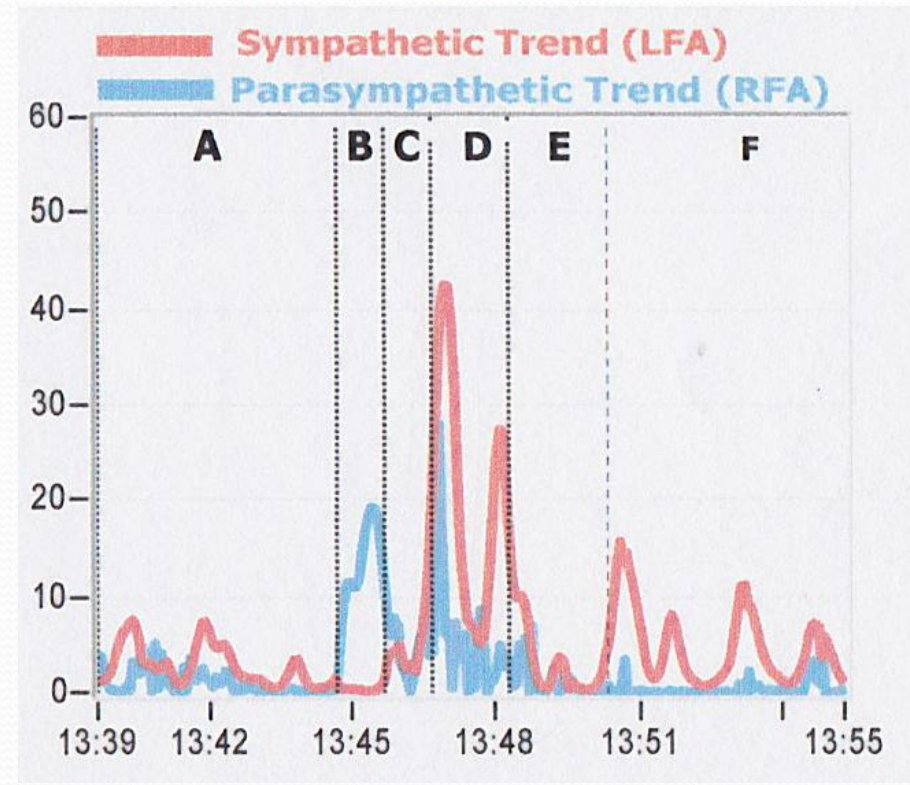
- Fluctuations can affect every body system:
  - Body temperature
  - Digestion
  - Breathing
  - Heart rate and blood pressure
- Sympathetic hyperactivity can aggravate pain and sleep problems, and mimic anxiety, panic, even hypomania
- Parasympathetic overactivity can cause nausea and aggravate fatigue, malaise, lightheadedness

# Sympathetic and Parasympathetic Activity Before and After Treatment

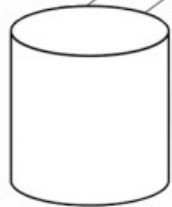
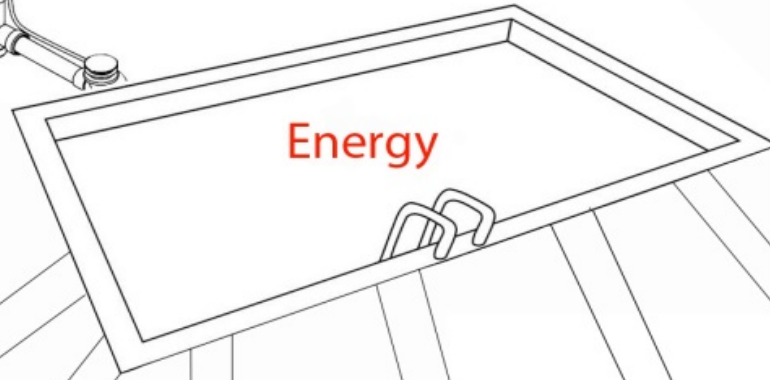
At Diagnosis



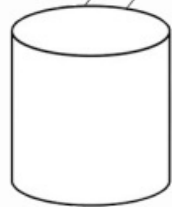
After 18 months of treatment



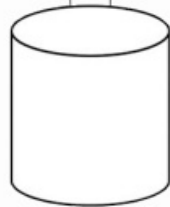
A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand



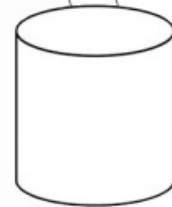
Pain



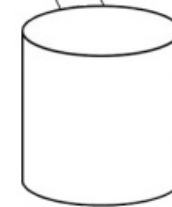
Fatigue



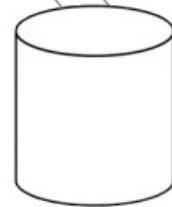
Dehydration



Cognitive  
Effort



Emotional  
Stress



Work/School  
Other



# ANS Dysfunction is Another 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=Total Concentration of Electrolytes, Proteins, etc. in the Blood
  - Normal ranges usually 280-300
  - Most people with orthostatic intolerance are around 280
- Urine Osmolality=Total Concentration of Urine
  - 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
- If you find that “water goes right through me,” or “no matter how much I drink I’m still thirsty,” you’re drinking TOO MUCH water!
- Forget conventional wisdom that salt is bad for you
- Most people don’t need more than 2-3 liters of fluid a day

# Mast Cell Dysfunction

- Now clearly associated with EDS
- Can cause respiratory, skin, and digestive problems
- Mast cell overactivity also can aggravate autonomic problems, fatigue, and pain
- Dietary measures and pharmacological measures are usually both necessary to control symptoms

# So How Do You Break The Cycle of Chronic Pain, Poor Sleep, Fatigue and Depression?

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



Energy

Pain

Fatigue

Dehydration

Cognitive  
Effort

Emotional  
Stress

Work/School  
Other



# Reverse the Vicious Cycle

Improved  
Mood

More  
Energy

Less Pain

Better  
Sleep



**And This Is How Ehlers-  
Danlos Patients Get Better!**

# Rest Break

