



PRESENTATION

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Rockville, Maryland
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SPEAKER

The Role and Treatment of Autonomic Dysfunction in EDS-Associated Sleep Disorders

Disclaimers

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

Overview

- Autonomic nervous system (ANS) regulates all involuntary body processes, and also plays a role in regulating sleep
- ANS dysfunction is very common in Ehlers-Danlos and other hypermobility-related syndromes, and underlies many of their symptoms
- The most common type of sleep disorder seen in the hypermobility syndromes appears to have an autonomic basis



“No rest even after counting the whole flock?
You should be tested for sheep apnea.”

Basics of the ANS

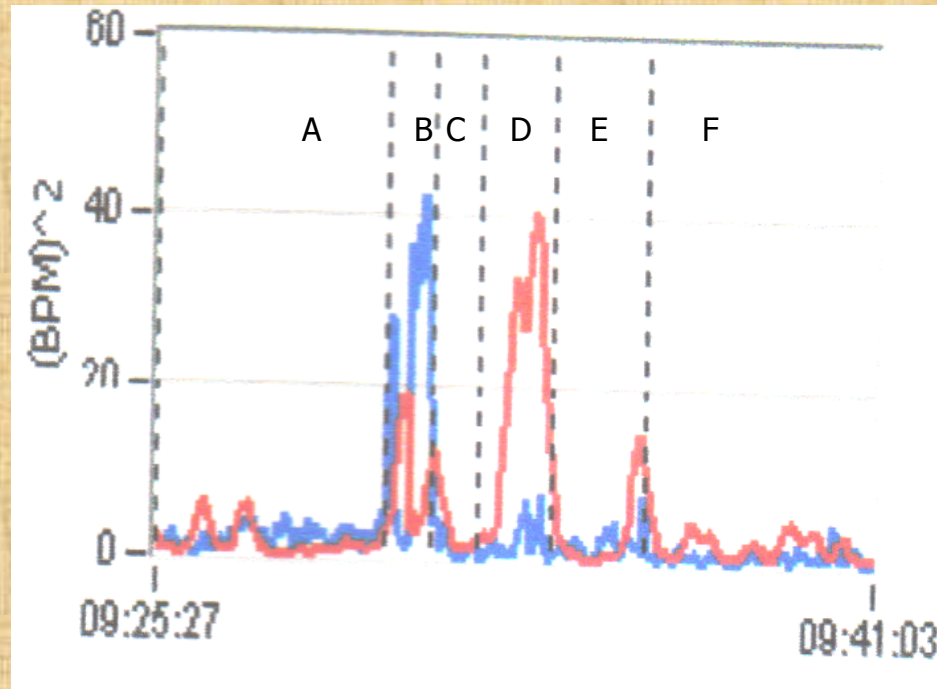
- Sympathetic nervous system: “fight or flight,” the accelerator
- Parasympathetic nervous system: “rest and digest,” the brake

Autonomic Instability

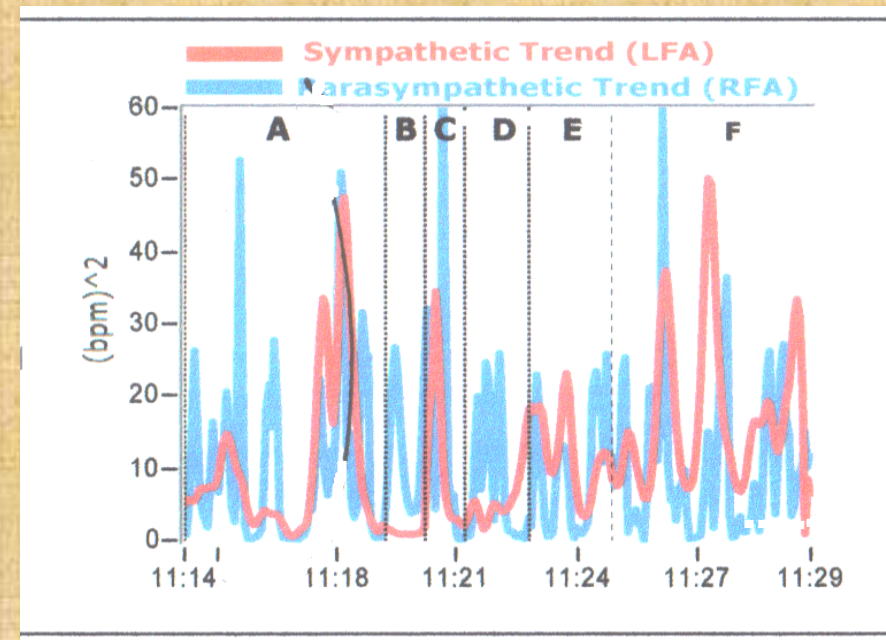
“Failure to Modulate”

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

Sympathetic and Parasympathetic Activity with Autonomic Maneuvers



Normal

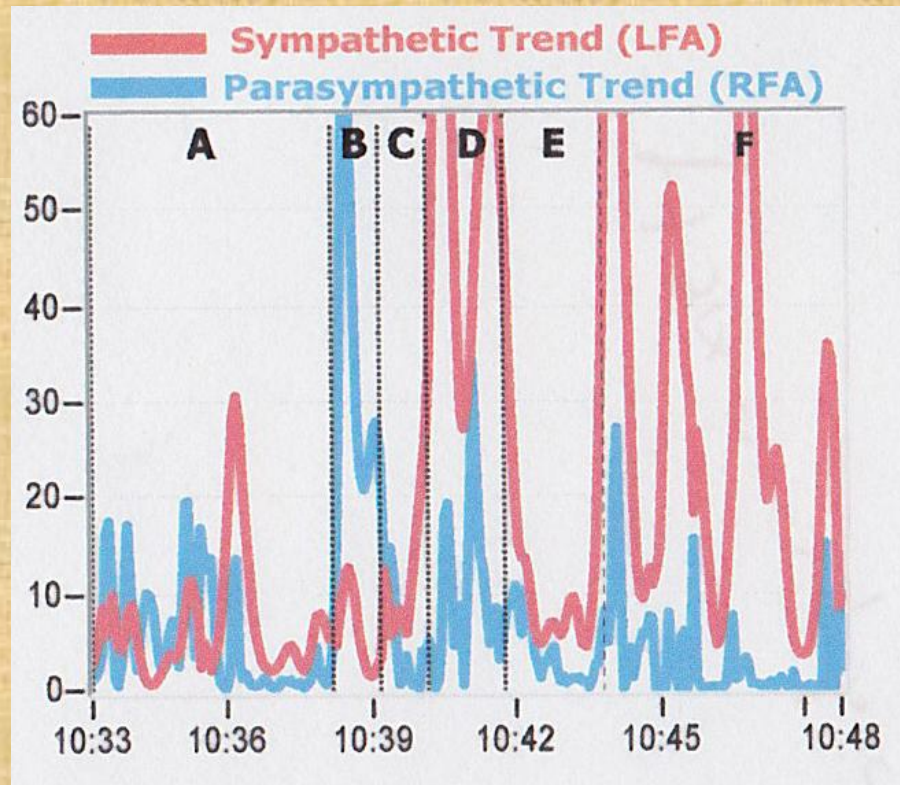


EDS with Dysautonomia

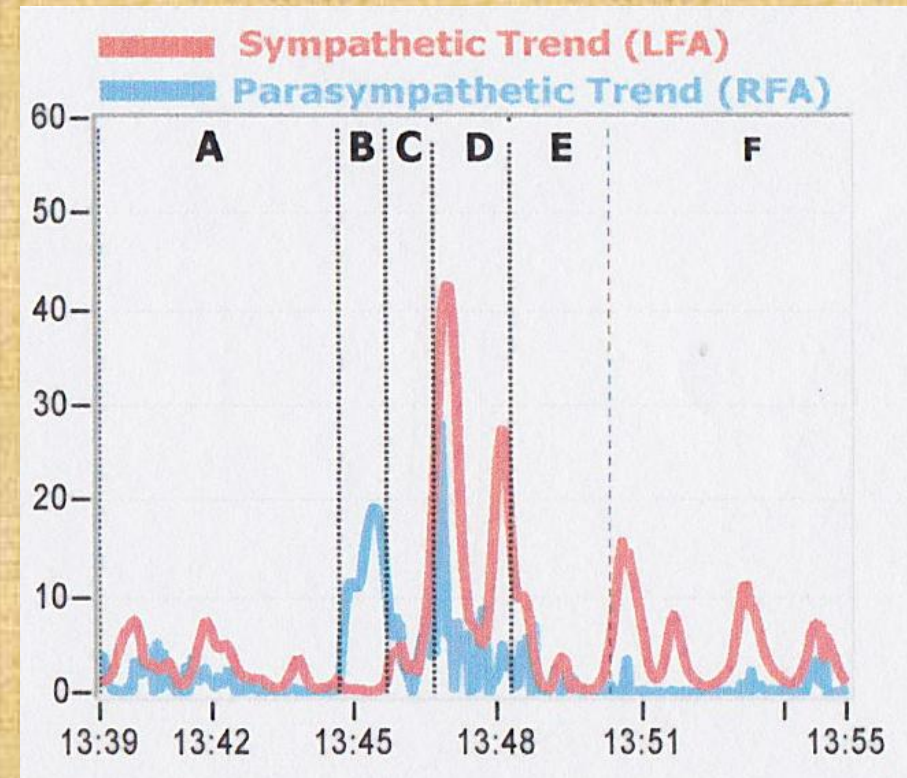
A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand

Sympathetic and Parasympathetic Activity Before and After Treatment

At Diagnosis



After 18 months of treatment



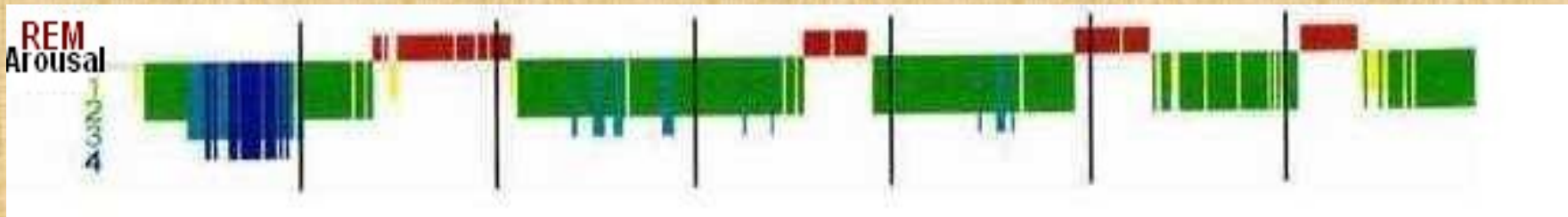
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Sleep “Misperception”

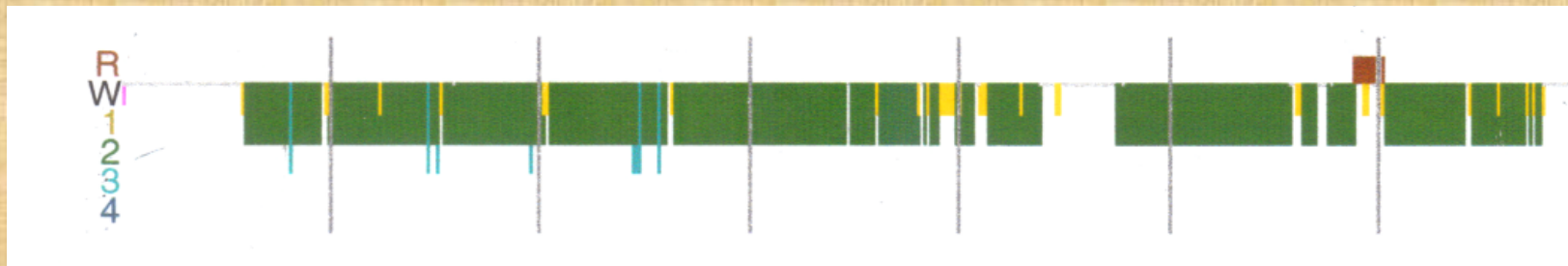
- Many EDS patients report that they “sleep fine.”
- “I’m a great sleeper. I can sleep any time, anywhere.”
- But... do you feel rested when you get up?
 - “No, I never feel rested.”
 - “I wake up feeling like I haven’t slept.”
 - “I don’t think I know what feeling rested would feel like.”
- Not just a problem in EDS, e.g. as many as 90% of people with sleep apnea are not aware of it

Non-Restorative Sleep in EDS

- Frequent arousals and awakenings
- Little or no deep sleep

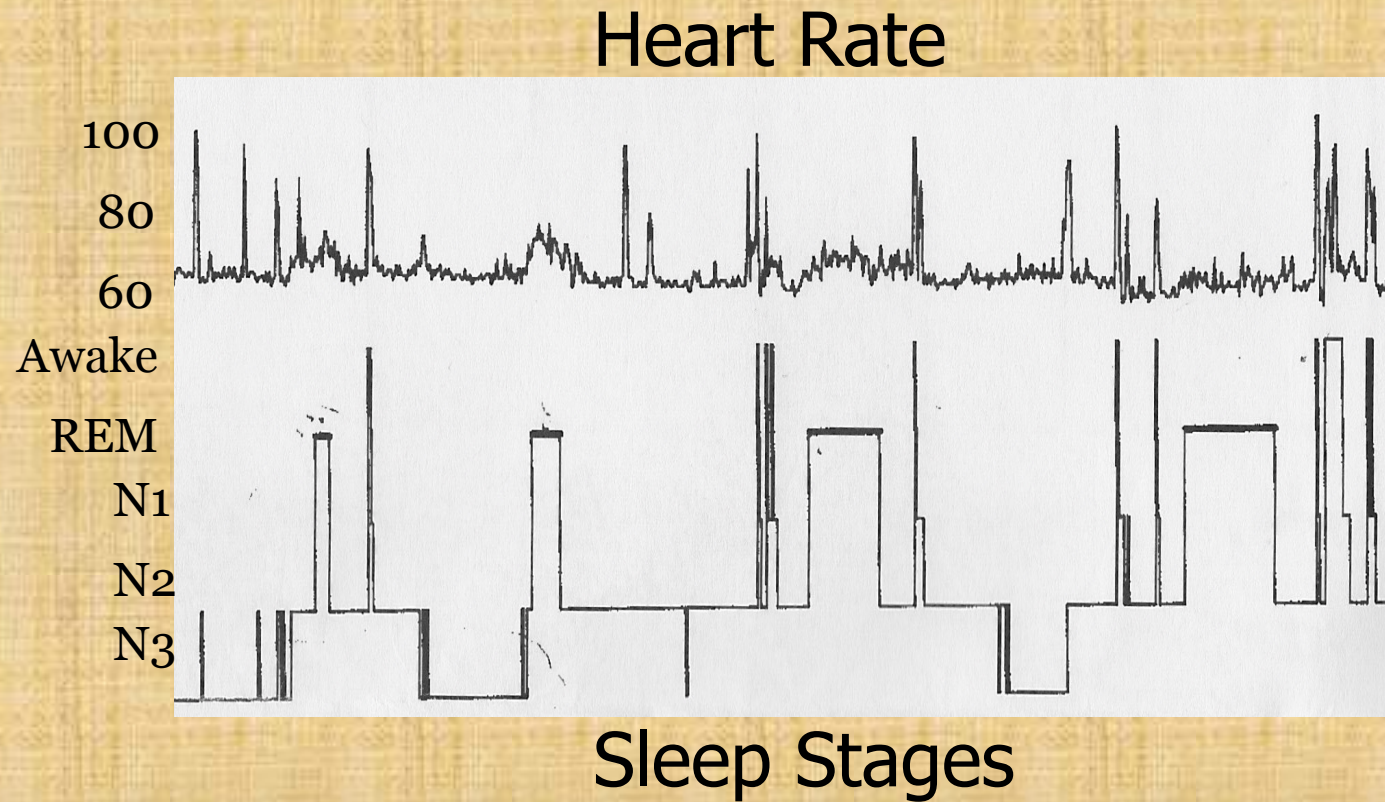


Normal Sleep

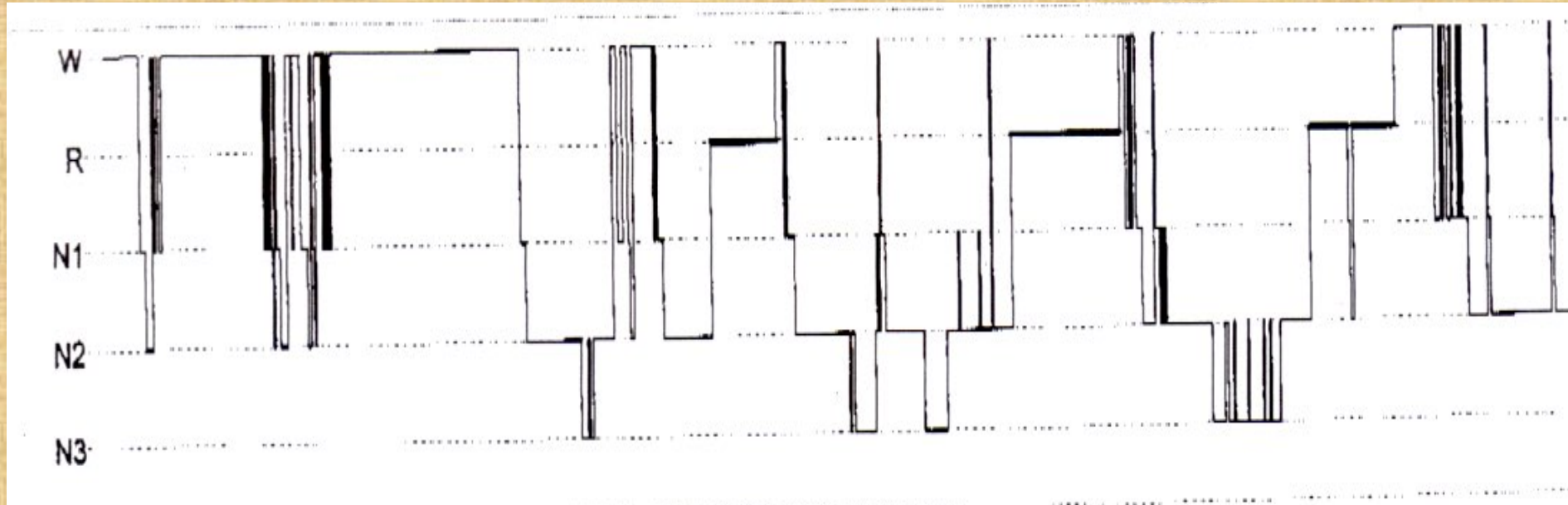


Non-Restorative Sleep

Heart Rate Fluctuations Associated with Sleep Disruptions



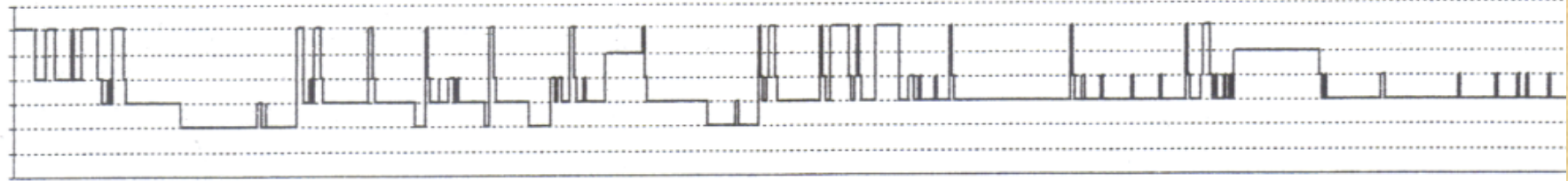
Sleep Stages



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

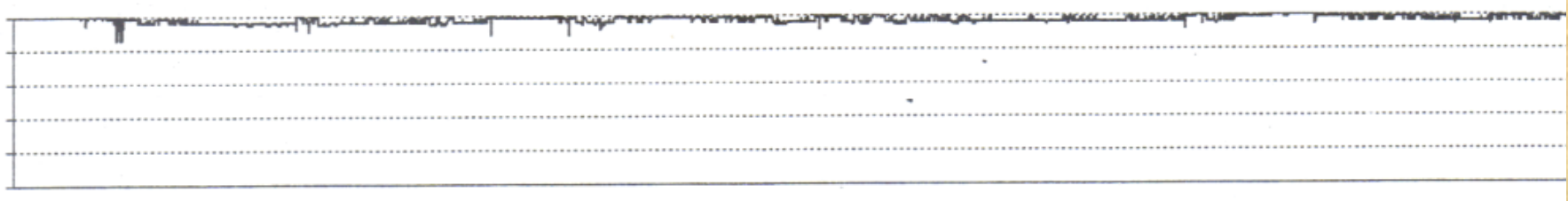
Hypnogram

W
R
N1
N2
N3
M



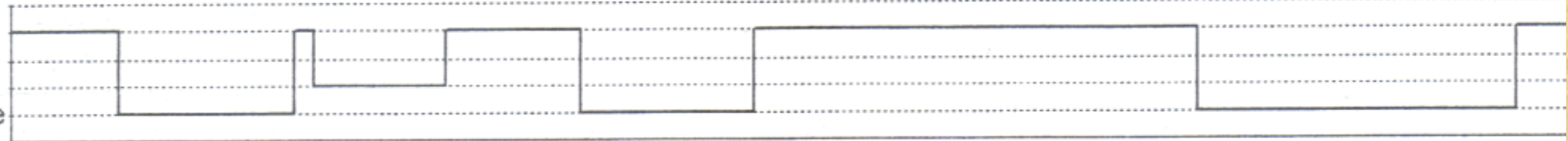
SaO2%

100
90
80
70
60
50



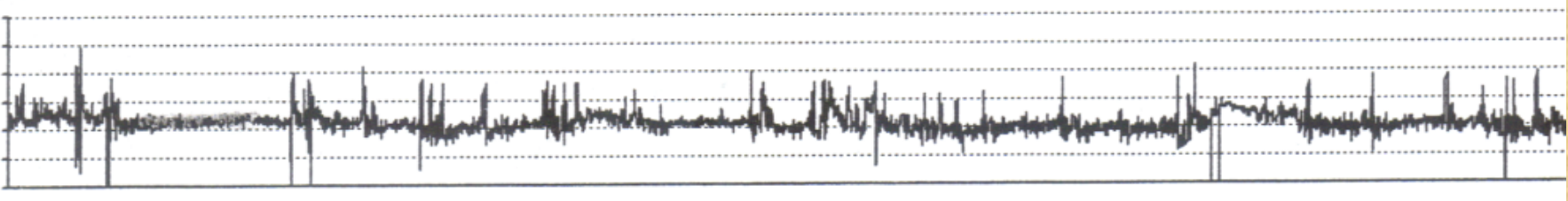
Body-Position

Supine
Left-Side
Right-Side



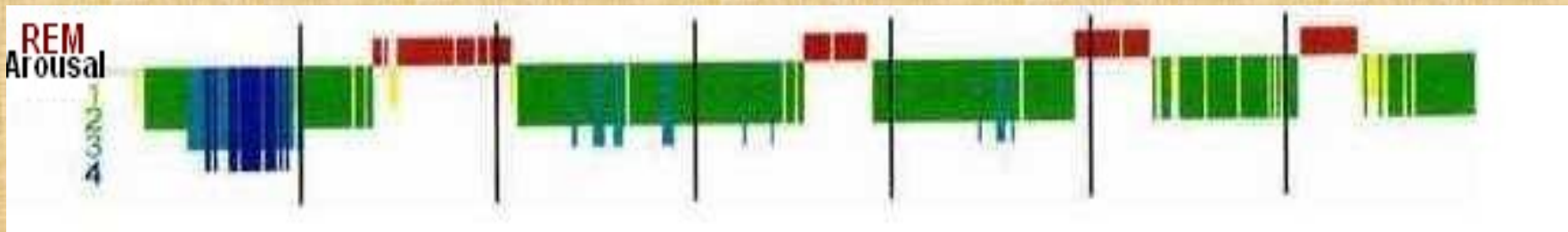
Heart Rate

BPM
150
130
110
90
70
50
30

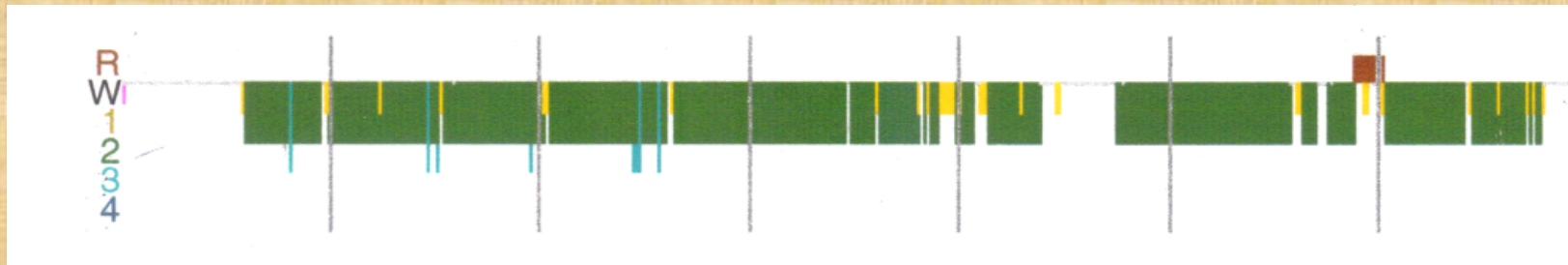


Non-Restorative Sleep

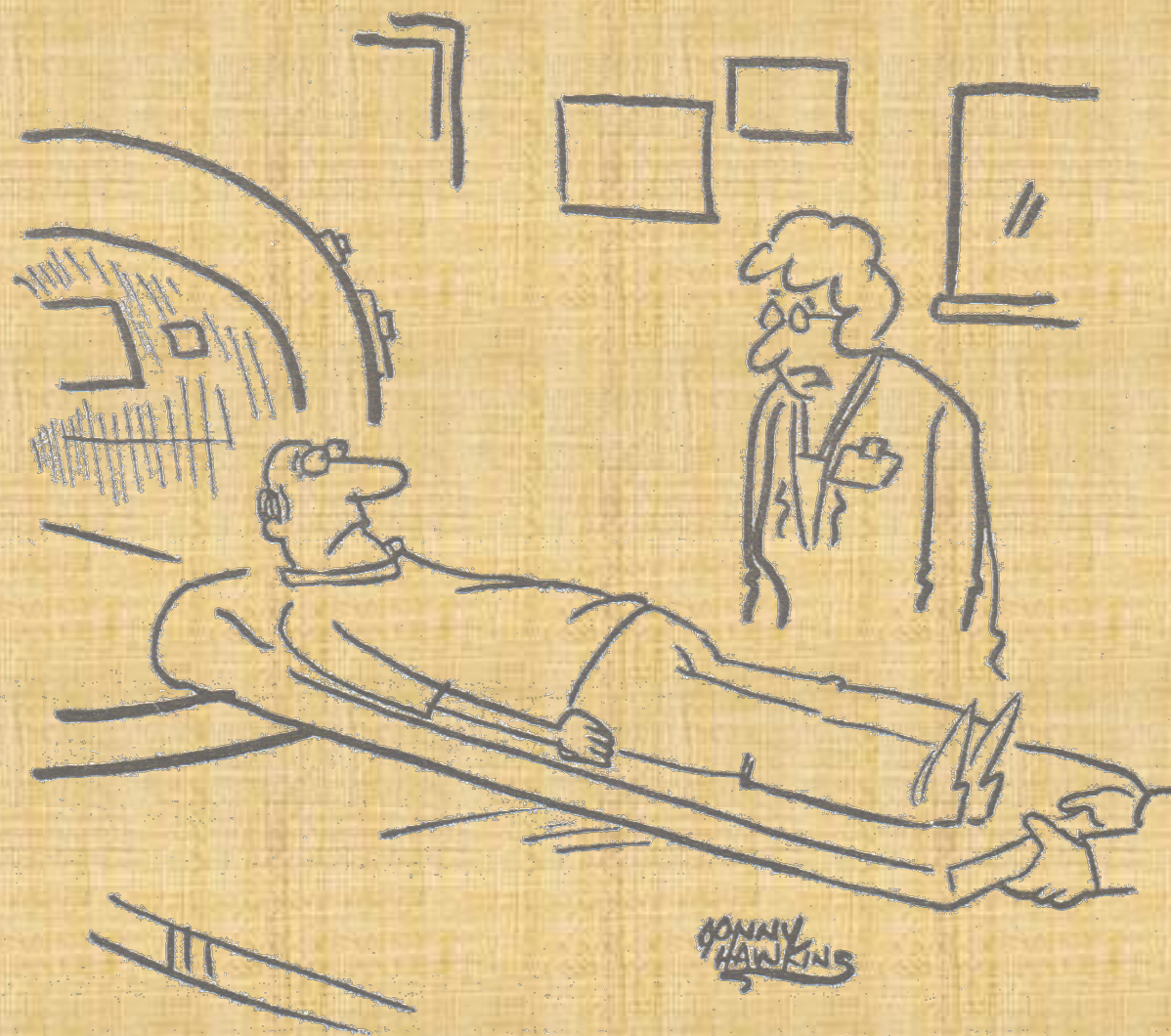
- Frequent arousals and awakenings
- Little or no deep sleep



Normal Sleep



Non-Restorative Sleep



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

“First-Night Effect”

- Well known that people often don't sleep well during their first night in a sleep lab, or in general in their first night in any new place
- Attributed to the “night watch” or “on alert” phenomenon, a protective mechanism to be “hypervigilant” for threats in a new environment
- In fact one part of the brain sleeps while another remains more alert even during sleep

“Night Watch in One Brain Hemisphere during Sleep Associated with the First-Night Effect in Humans*”

- Interhemispheric asymmetry of sleep depth
- First-night effect is a manifestation of one hemisphere being more vigilant than the other as a “night watch” to monitor unfamiliar surroundings during sleep
- The degree of asymmetry was significantly correlated with how long it took to fall asleep
- The hemisphere with reduced sleep depth showed enhanced evoked brain response to deviant external stimuli, which caused more arousals and faster behavioral responses than those detected by the other hemisphere, but...

- In this study of healthy people:
 - “None of these asymmetries was evident during subsequent sleep sessions”*
- While in Ehlers-Danlos and related conditions:
 - It seems as if every night is a “First Night!”

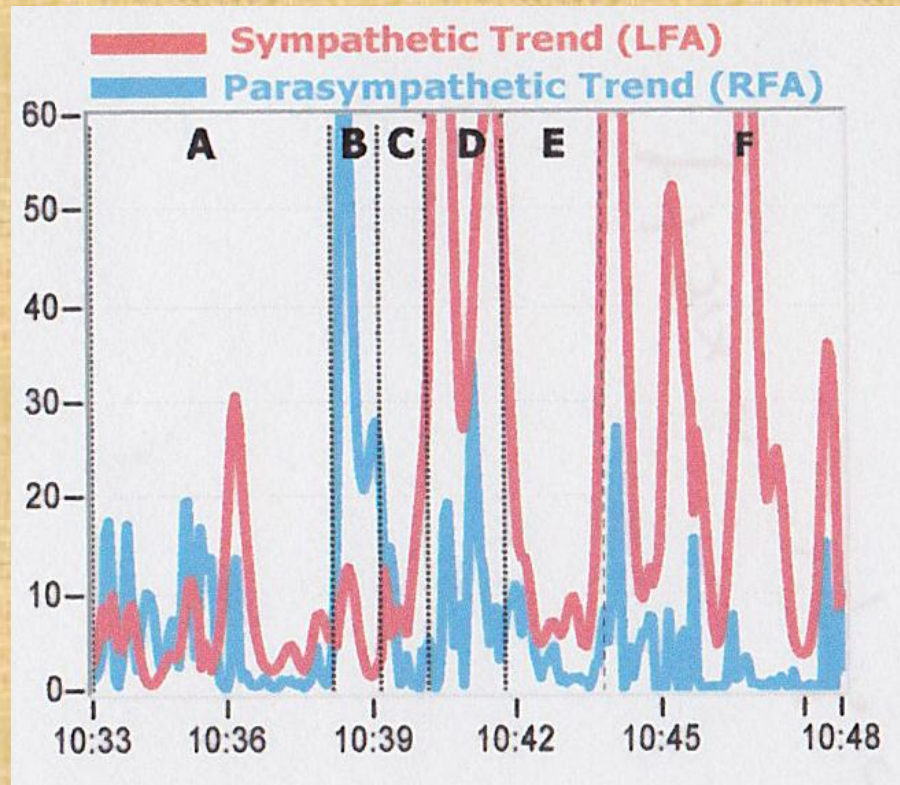
*TamakiM, BangJW, WatanabeT, SasakiY. Current Biology, 26(9):1190-1194, 2016

To Improve Sleep, You Need
to Improve Autonomic
Function

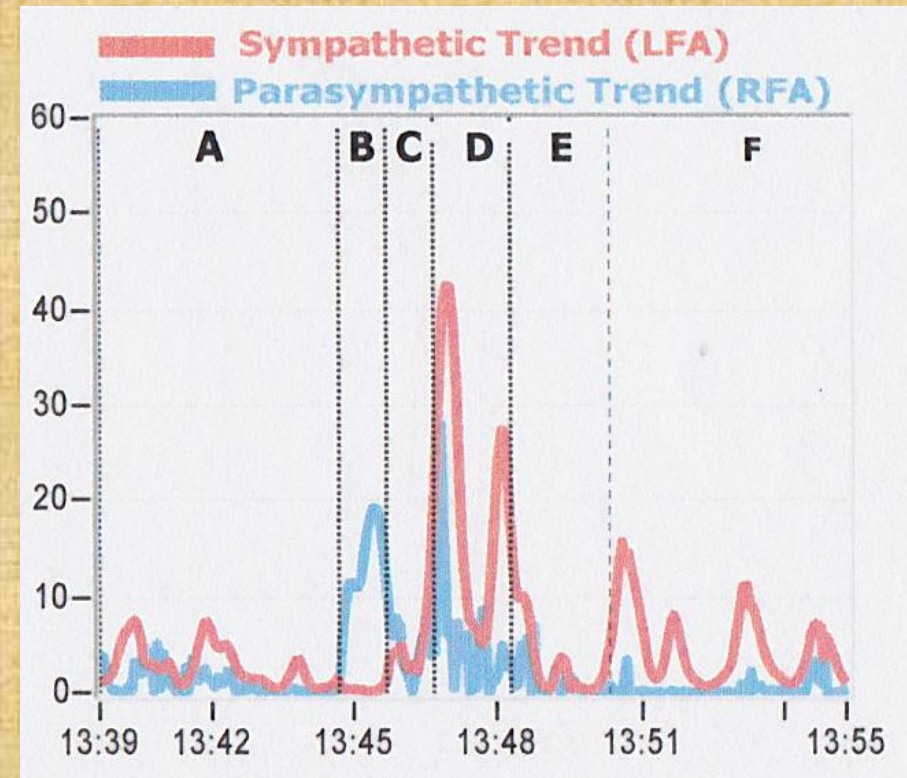
And to Improve Autonomic
Function, You Need to
Improve Sleep

Sympathetic and Parasympathetic Activity Before and After Treatment

At Diagnosis



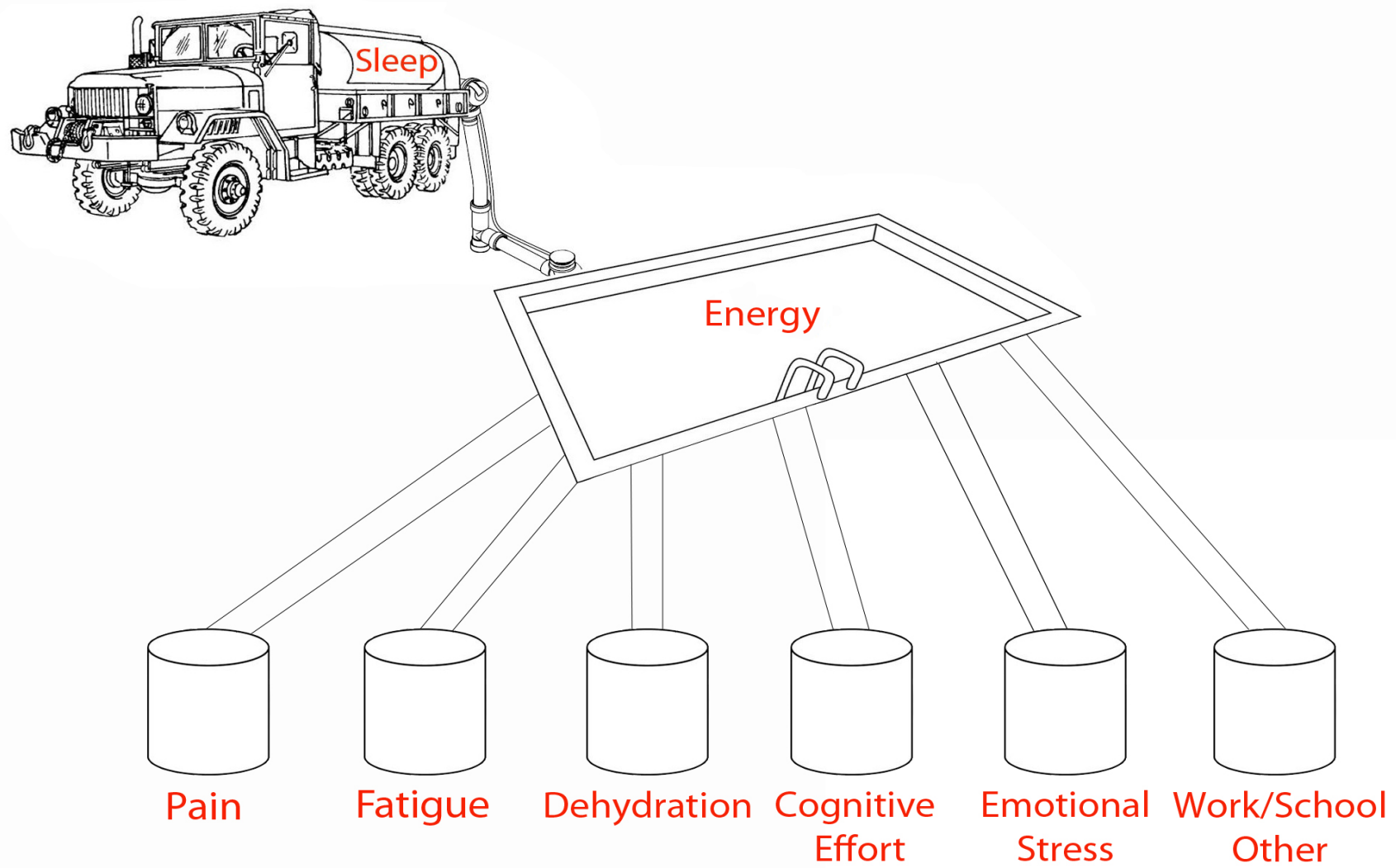
After 18 months of treatment



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

Treatment of Non-Restorative Sleep

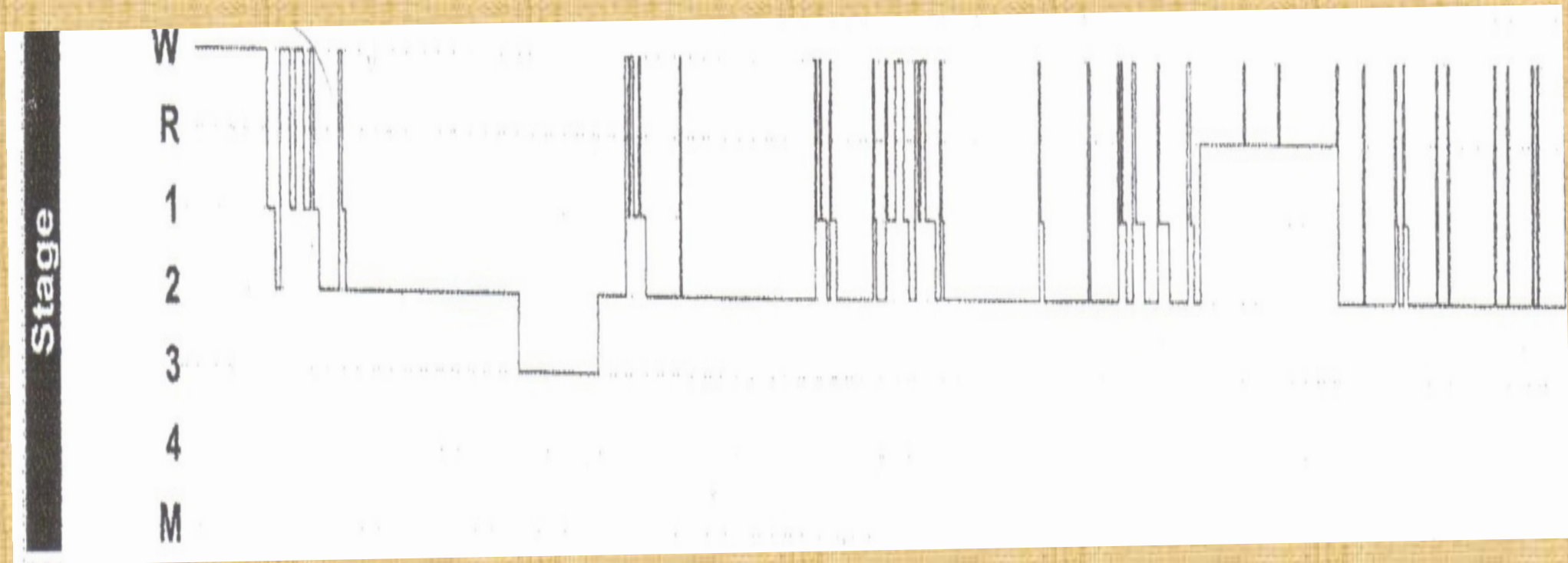
- Address underlying causes of autonomic dysfunction:
 - Pain
 - Fatigue
 - Dehydration
 - Low blood sugar
 - Emotional/cognitive stresses



Restoring Autonomic Balance, or Refilling the Pool

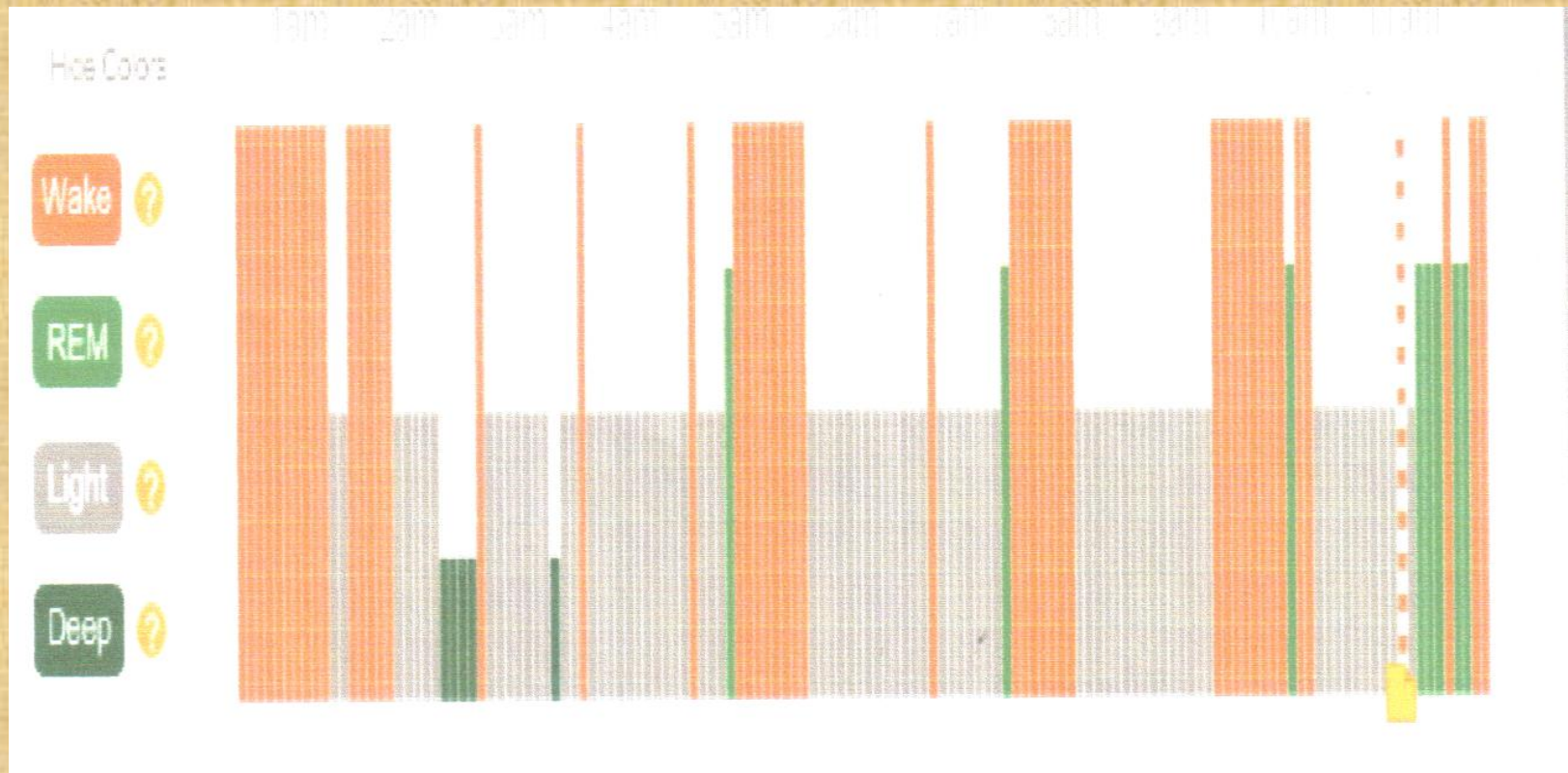
- Better sleep—quantity and quality
- Adequate—really—pain control
- Don't “push through” fatigue; take breaks
- Adequate salt and fluid
- Avoid hypoglycemia
- Minimize emotional and other stresses

EDS, Untreated (Sleep Lab)

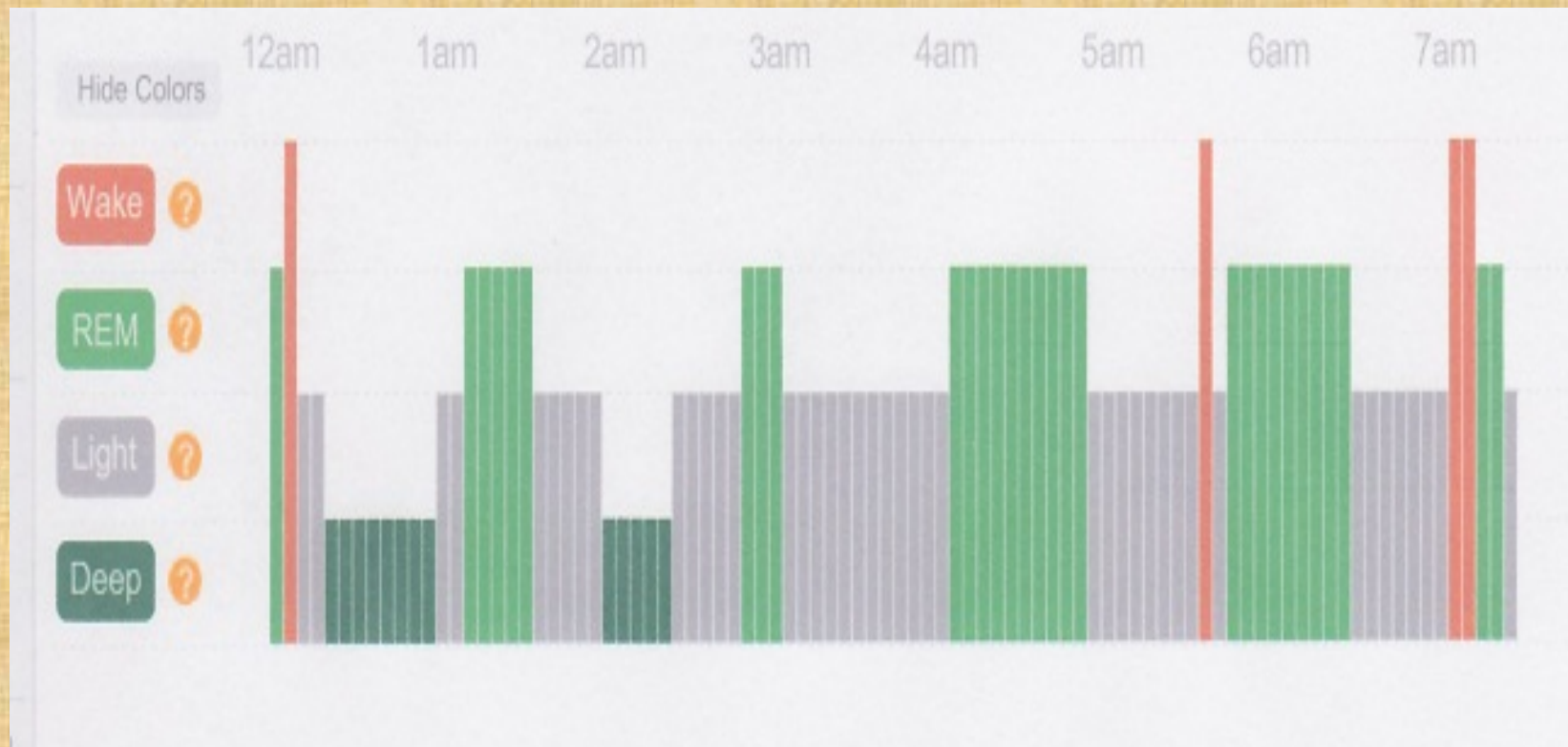


EDS, Untreated

(Same Patient, Home Sleep Monitor)



EDS, After Treatment (Home Sleep Monitor)



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



“No rest even after counting the whole flock?
You should be tested for sheep apnea.”

Non-Pharmacologic Treatment of Sleep Disorders

- CPAP/AutoPAP or dental appliances for apnea
- Guided imagery
- Deep Breathing
- Sequential relaxation
- White/pink noise
- Avoid alcohol!

Treatment of Sleep Disorders: Medication

- Block/prevent extra adrenaline (beta and alpha blockers, clonidine and guanfacine)
- Block histamine (diphenhydramine, hydroxyzine)
- Reduce arousal (benzodiazepines; orexin inhibitors, e.g. suvorexant)
- Reduce pain (analgesics, muscle relaxants, gabapentin, pregabalin)
- Increase deep sleep (trazodone, doxepin, mirtazepine)
- Use “Sleeping pills” sparingly

Beta Blockers

- Propranolol
 - Start with 10 mg at bedtime
 - Increase by 10 mg every 4-5 days until fewer awakenings, side effects, or no further benefit
 - Switch to long-acting if needed
 - Take some earlier if needed to offset 'second wind'
 - Often need smaller daytime dose as well
 - If ineffective or not tolerated, try a different beta blocker

Other Beta Blockers

- Metoprolol
 - Start with half a 25 mg tablet (metoprolol tartrate)
 - Increase by half a tablet every 4-5 days
 - Add long-acting (metoprolol succinate) for daytime symptoms
- Nadolol
 - Lasts longer, so take before evening “second wind”
 - Start with 20 mg. increase by 20 every 4-5 days
 - Add smaller AM dose if needed for daytime symptoms
- Carvedilol
 - Start with 3.125 mg, increase by one tablet every 4-5 days
 - Add smaller AM dose if needed for daytime symptoms
- Nebivolol
 - Once daily, often well tolerated when others aren't

Clonidine/Guanfacine

- Clonidine
 - Start with 0.1 mg at bedtime
 - Increase by 0.1 mg no sooner than one week
 - No more than 0.3 mg
 - Usually lasts about 6 hours
 - 24/7 topical patch for constant sympathetic hyperarousal
- Guanfacine
 - Very similar to clonidine but lasts longer
 - Also marketed as Intuniv™ for ADD

Alpha Blockers

- Prazosin best studied, shown to reduce nightmares in PTSD, where “a hypersensitivity to adrenaline triggered many of their nightmares.” In a VA study, 75-80% of PTSD patients stopped having nightmares after being treated with prazosin.
- Start with 1 mg, increase gradually; usual dose is about 5mg, but average dose in VA study was about 10 mg.
- Can worsen orthostatic intolerance, but uncommonly.
- Other alpha blockers, terazosin and doxazosin, appear to have similar benefits, but doxazosin causes more lightheadedness. Combination alpha-beta blockers (e.g. carvedilol) don't seem to be as effective.

Benzodiazepines

- All have beneficial properties:
 - Sedative
 - Anti-anxiety
 - Muscle relaxant
 - Anti-movement, anticonvulsant
 - “Anti-adrenaline”
- But also potential problems:
 - Impair cognition, motor performance
 - Depress mood, respiration
 - Cause or worsen fatigue
 - Tolerance, Dependence, Withdrawal

Some Common Benzodiazepines

- Clonazepam (Klonopin™)
 - Longest-lasting, most likely to have residual effects
 - Also effective for restless leg, PLMS
- Diazepam (Valium™)
 - Typically lasts about 8 hours
 - Probably best muscle relaxant
- Temazepam (Restoril™)
 - Typically lasts about 7 hours
 - Capsule limits dosage adjustment
- Lorazepam (Ativan™)
 - Typically lasts about 6 hours
 - Metabolized differently (less variability, interactions)

Analgesics

- Anti-inflammatories
 - NSAIDs: Ibuprofen, Naproxen, Meloxicam, Celecoxib, etc
 - Avoid prednisone (tends to cause/worsen insomnia)
- Acetaminophen; Tramadol, short- and long-acting
- Opioids, short-, long-acting; patches (fentanyl, buprenorphine)
- Duloxetine (Cymbalta™), Milnacipran (Savella™)
- Gabapentin (Neurontin™), Pregabalin (Lyrica™)
- Lidocaine patch; diclofenac patches, gel, and solution

Muscle Relaxants

- Cyclobenzaprine (Flexeril™)
 - Shown to improve sleep quality in fibromyalgia
 - Has analgesic, sedative, muscle relaxant properties
- Carisoprodol (Soma™)
 - Less sedating, ? more analgesic effect, especially with narcotics, but might be habit-forming and depress mood
- Metaxolone (Skelaxin™), chlorzoxazone (Lorzone™)
 - Less sedating, some can tolerate daytime doses
- Tizanidine (Zanaflex™)
 - More sedating, high margin of safety
- Lioresal (Baclofen™)
 - Potent, for neurological spasm, not recommended for musculoskeletal pain

Antidepressants

- SSRI's often cause shallower sleep, more dreams
 - Fluoxetine (Prozac™) worst, Lexapro™ best
 - Use lowest effective dose, consider liquid formulations
- Duloxetine (Cymbalta™) also relieves pain, sleep neutral if taken in AM
- Fetzima™/Savella™ also have pain and mood effects
- Tricyclics, e.g. amitriptyline, generally improve sleep, but often cause daytime sedation at antidepressant doses
- Bupropion (Wellbutrin™) impairs sleep if taken late in day, so take once-daily (XL) form early in day or consider AM only dosing or AM and early PM dosing of twice a day (SR) form
- Ramelteon (Remeron™) can improve sleep; also can improve appetite and cause weight gain

Other Agents

- Trazodone
 - Probably most effective at increasing deep sleep
 - Low dose, 50-150 mg, most people take 50 mg
- Amitryptiline
 - Seems to improve sleep quality, especially with pain
 - Start at 10 mg, most people take 20-40 mg
- Doxepin
 - Enhances sleep more at lower doses
 - 10 mg tablet, liquid, or Silenor™ 3 mg, 6 mg
- Antihistamines, e.g hydroxyzine, diphenhydramine

“Sleeping Pills”

- Zolpidem, short- and long-acting
 - Doesn't reduce arousals or improve sleep architecture
 - Use for onset/maintenance only if needed, e.g. until other meds effective
 - Can cause retrograde amnesia
 - Zolpidem usually lasts 5 hours, ER about 7
- Eszopiclone
 - Doesn't seem to reduce arousals or improve sleep architecture
 - Occasionally helps with sleep onset and maintenance, e.g. until other medications become effective, or in combination with other medications
 - Usually lasts about 7 hours
- Zaleplon
 - Good for sleep onset, or getting back to sleep
 - Lasts 2-3 hours, no cognitive impairment
- Melatonin/Ramelteon
 - Occasionally helpful for Circadian problems e.g. evening “second wind”

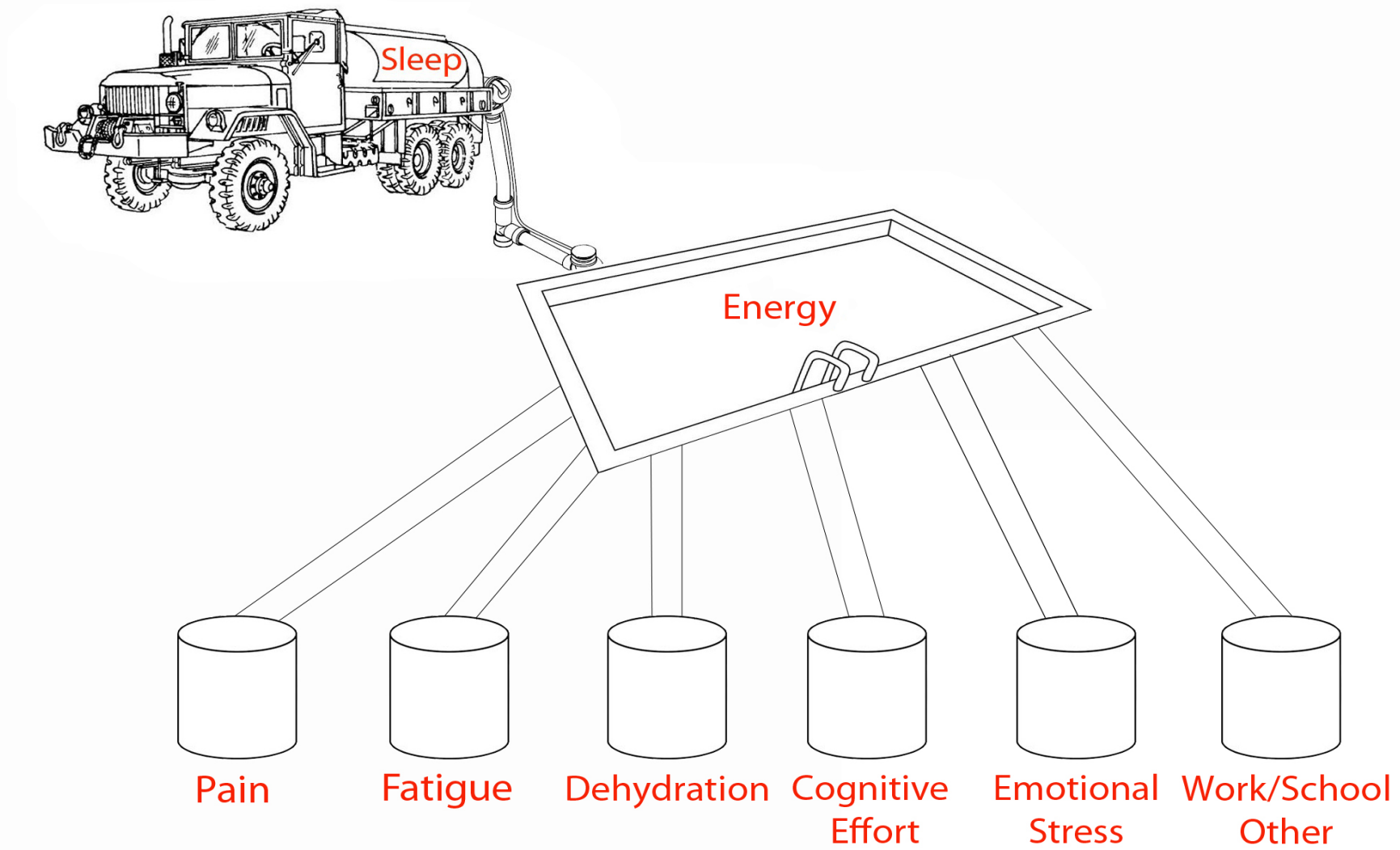
DO YOU HAVE ANY DATA?

ONLY THE TWO-LEGGED KIND!

- “I am stunned, amazed, and grateful at the benefits of taking propranolol. The improvement in my sleep quality alone is fantastic.”
- “The medicine you gave me is amazing. Two worked great but three worked even better. I forgot to take it one night and slept 12 hours and felt terrible. The next night I took it and slept 6 hours and felt great.”
- “The metoprolol seems to help considerably with my sleep. In fact, between metoprolol, flexeril, and good old advil, I’m able to fall asleep and stay asleep. The metoprolol really seems to be particularly important for quality of sleep.”
- “I just wanted to let you know again how much the Prazosin helps me. I am sleeping better now than I ever have in my life. If I get 7 hours of sleep, it's always uninterrupted and I awake feeling rested and ready for the day. It's changed my life!”

Summary

- The most common type of sleep disorder seen in the hypermobility syndromes appears to be characterized by excessive sympathetic activity at night.
- Medications to suppress, offset, or block this excessive activity are effective in improving sleep quality, as measured both by sleep study data and symptom relief.



Summary (continued)

- Improving sleep and minimizing daytime stresses helps to replenish autonomic reserves, which in turn improves daytime autonomic balance and also helps improve sleep, which in turn improves daytime function, which in turn improves circadian rhythms and sleep, which

IS HOW PEOPLE GET BETTER!

Acknowledgements

EDS for inviting me, and for helping to spread knowledge and understanding

Dr. Peter Rowe and Dr. David Goldstein for encouraging me when others thought I was nuts

Dr. Clair Francomano, Dr. Fraser Henderson, and Dr. Rodney Grahame for teaching me about EDS and stimulating my interest in it

All my patients, for having the confidence in me to let me experiment on them and learn from them!

Understanding Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorder

(previously known as Ehlers-Danlos syndrome hypermobility type & joint hypermobility syndrome, respectively).

by Claire Smith



Disjointed

Navigating the Diagnosis and Management of
hypermobile Ehlers-Danlos Syndrome and
Hypermobility Spectrum Disorders

Edited by Diana Jovin



Thank you
for listening