SLEEP DISTURBANCES
ME/CFS and FM

Lucinda Bateman MD
Bateman Horne Center
2018

Behavioral Objectives Session 4: Restorative Sleep

The participant will be able to :

- Investigate **sleep disturbances** and determine if **non-restorative sleep** is a core feature of illness.
- Utilize existing resources to screen for primary sleep disorders and treat them if present.
- Create a treatment plan for improvement of restorative sleep based on clinical presentation.

Alternate "new" Fibromyalgia Criteria (ACR 2010)

1) Widespread PAIN index (WPI)

(0-19 points—see next slide)

2) Symptom Score (SS):

0=none, 1=mild, 2=mod, 3=severe

Chronic fatigue	(0-3)
Unrefreshing sleep	(0-3)
Cognitive complaints	(0-3)
Multisystem complaints	(0-3)
Max SS = 12	

7+ 5+ FM

or 3-6 and 9+ FM

> 3 months in duration and without other apparent explanation

Wolf F, et al. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. Arthritis Care & Research. Vol. 62, No. 5, May 2010, pp 600–610

ME/CFS Evidence Based Clinical Diagnostic Criteria 2015:

Myalgic encephalomyelitis/Chronic Fatigue Syndrome

CORE criteria* (all are required for diagnosis)

1) **Impaired function** related to exhaustion/fatigue/low stamina
2) **PEM:** post exertional malaise (illness relapse)
3) **Unrefreshing sleep**
4) A. **Cognitive impairment** and/or
   B. **Orthostatic intolerance**

***Must be moderate-severe and frequent (present >50% of the time)**

Other common features of illness

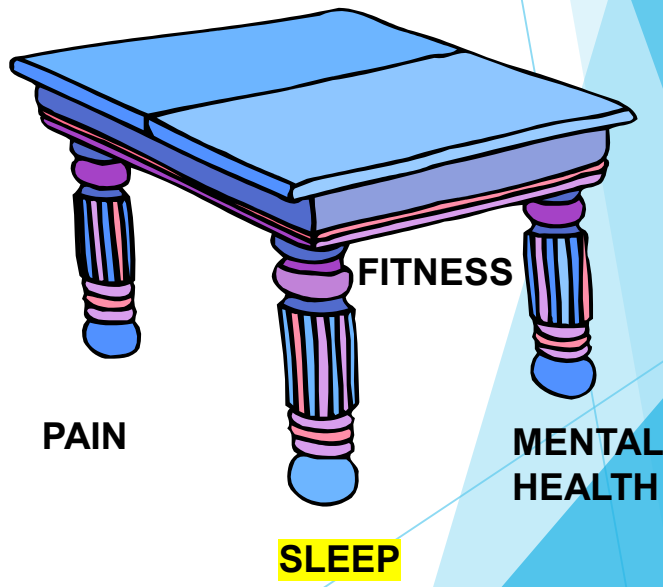
---**Pain** of all types
---**Immune manifestations** (allergy, inflammation, sensitivities)
---**Infection** (viral or atypical)
---Neuroendocrine dysregulation

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness.
Editors: Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb

General Principles of Supportive Management:

- **1) Address all other conditions** (complete a good medical work-up)
  - i.e. anemia, thyroid, diabetes, sleep apnea, low Vit B12, OSA, RLS
- **2) "Pace"** to prevent symptom escalation (Preventive activity management. Reduce overload)
- **3) Address the major aspects of illness**
  - PAIN: reduce severe pain
  - SLEEP: achieve restorative sleep
  - MENTAL HEALTH: insight and support
  - FITNESS: engage in restorative exercise



Unrefreshing sleep

- Sleep disturbances are common
  - Included in all CFS ME/CFS, ME and FM case definitions or symptom criteria
  - Present in >90% of all diagnosed
- Sleep abnormal in
  - Quality (light, restless, interrupted, heavy)
  - Duration/timing (delayed, prolonged, irregular)

*Abnormalities of sleep in patients with the chronic fatigue syndrome. British Medical Journal 306(6886):1161-1164. Morris et al. 1993

SLEEP

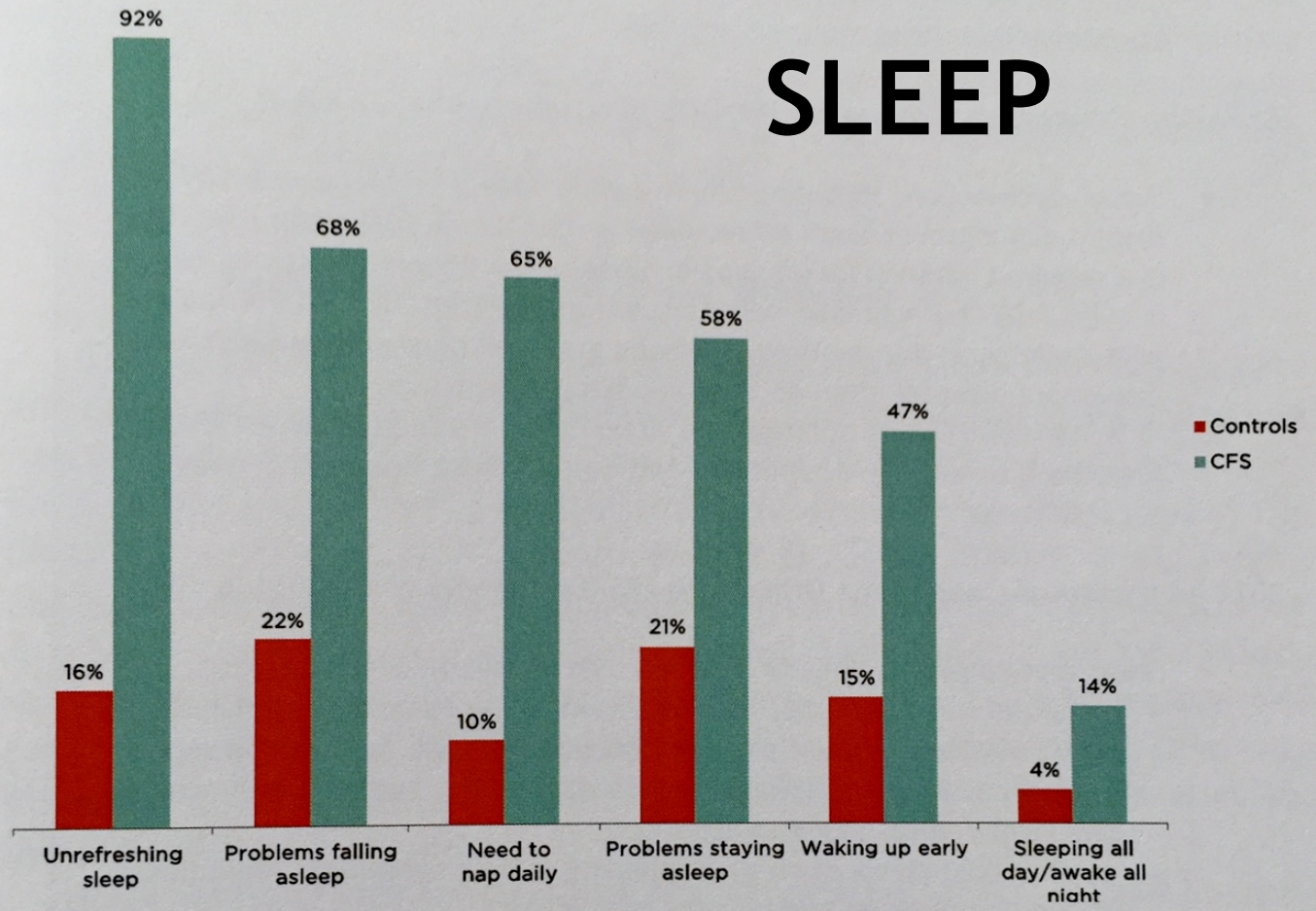


FIGURE 4-2 Percentage of ME/CFS patients and healthy controls reporting sleep-related symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.
SOURCE: Jason et al., 2013b.

Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. Jason LA, et al. Fatigue: Biomedicine, Health and Behavior 2(1) 2013.

ME/CFS research of special interest related to sleep:

1. **Polysomnography (sleep studies)**
2. **Central sensitivity, sensory amplification and hyperalgesia**
3. **Autonomic nervous system**

   Sympathetic : Parasympathetic
4. **HPA-axis (hypothalamus-Pituitary-Adrenal …)**

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

1. Polysomnography (PSG)

- PSG reveals Primary Sleep Disorders—need treatment
- PSG is otherwise non-diagnostic in ME/CFS and FM
  - Increased alpha (dozing, light sleep)
  - Decreased delta (slow wave, deep sleep)
  - Fragmentation
  - Delayed onset

Sleep Structure and sleepiness in chronic fatigue syndrome with oru without coexisting fibromyalgia. Arthritis Research & Therapy 10(3):R56. Togo 2008,
Are patients with chronic fatigue syndrome just "tired" or also "sleepy"? Neu et al 2009. Journal of Sleep Research 17(4):427-431
Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis. A review. Jackson et al 2012. Journal of Clinical Sleep Medicine. 8(6):719-728

Primary Sleep Disorders

- Central sleep apnea
- Obstructive sleep apnea
- Movement disorders (RLS, PLMD)
- Narcolepsy

Obviously cause severe sleep disruption, somnolence, fatigue and other symptoms. Primary sleep disorders are commonly seen in ME/CFS and FM patients*.

*How significant are primary sleep disorders and sleepiness in the chronic fatigue syndrome? Sleep Research Online 3(2):43-48. LeBon 2000

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Challenges of interpreting ME/CFS and FM sleep research using PSG

Sleep study “artifact” confounds interpretation.

- Since sleep architecture may be altered by the PSG testing itself, primary illness is not easily assessed

Abnormal sleep architecture may be the main presenting disturbance of ME/CFS and FM.

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Primary sleep disorders and ME/CFS

- Treating primary sleep disorders may or may not help the symptoms of ME/CFS (Libman et al 2009, IOM report)
- Studies comparing clinical presentation of ME/CFS patient with and without sleep disorders have found no differences between the two groups (Le Bon et al 2000, Libman et al 2009, IOM report)
- There is evidence to suggest that primary sleep disorders should be considered important co-morbid conditions. There is little evidence that treatment of primary sleep disorders improves ME/CFS symptoms. (IOM summary in sleep section)

Other challenges of interpreting ME/CFS and FM PSG results

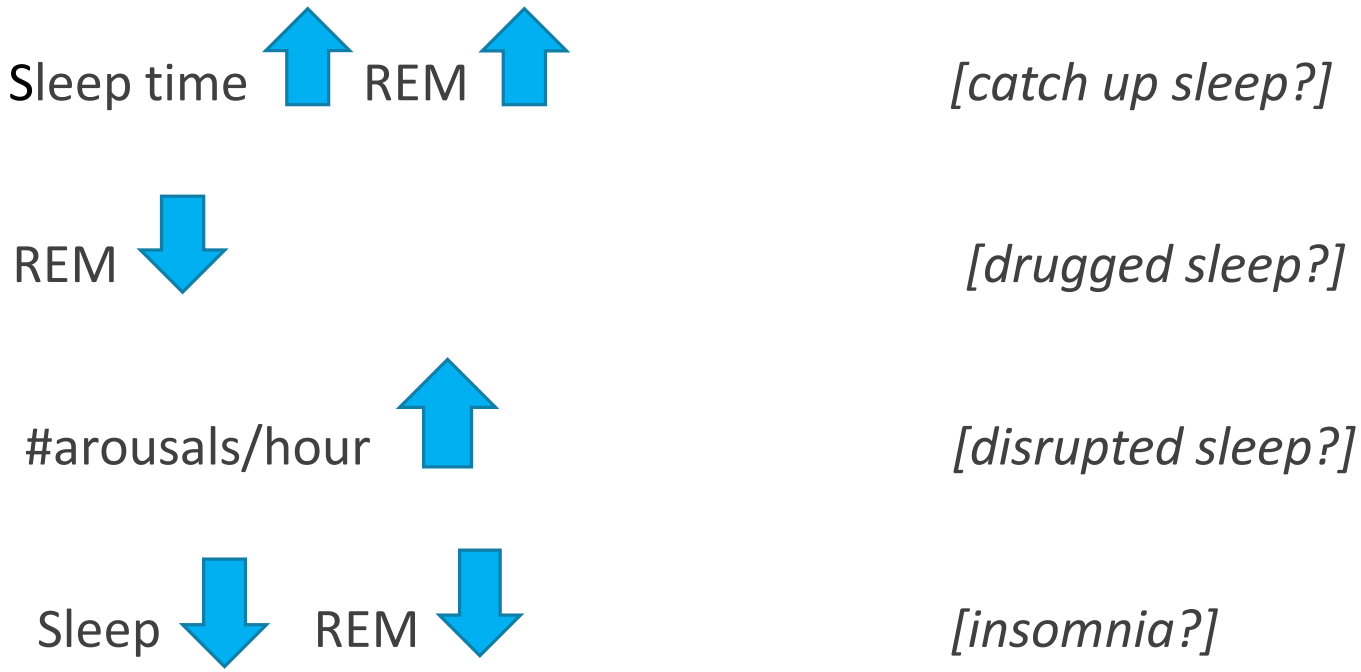
- Use of medications and withdrawal of medications alter sleep architecture (may need 1-2 weeks or more?)
- Stages of illness might have different sleep issues (especially in ME/CFS)
  - Initial hypersomnia---→later insomnia.
- Presence and severity of PEM? (in a crash or best-rested state?)
- Fear of insomnia and the ill consequences of insomnia
- Confounding conditions (menopause, PMS, low ferritin, stressors, presence or absence of pain, obesity, fitness…)

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Polysomnography 300 Dutch ME/CFS patients:

(those with primary sleep disorders excluded)

Four types of sleep presentation (1 PSG):



Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. BMJ Open. 2013;3(6):e002999

Who should get PSG?

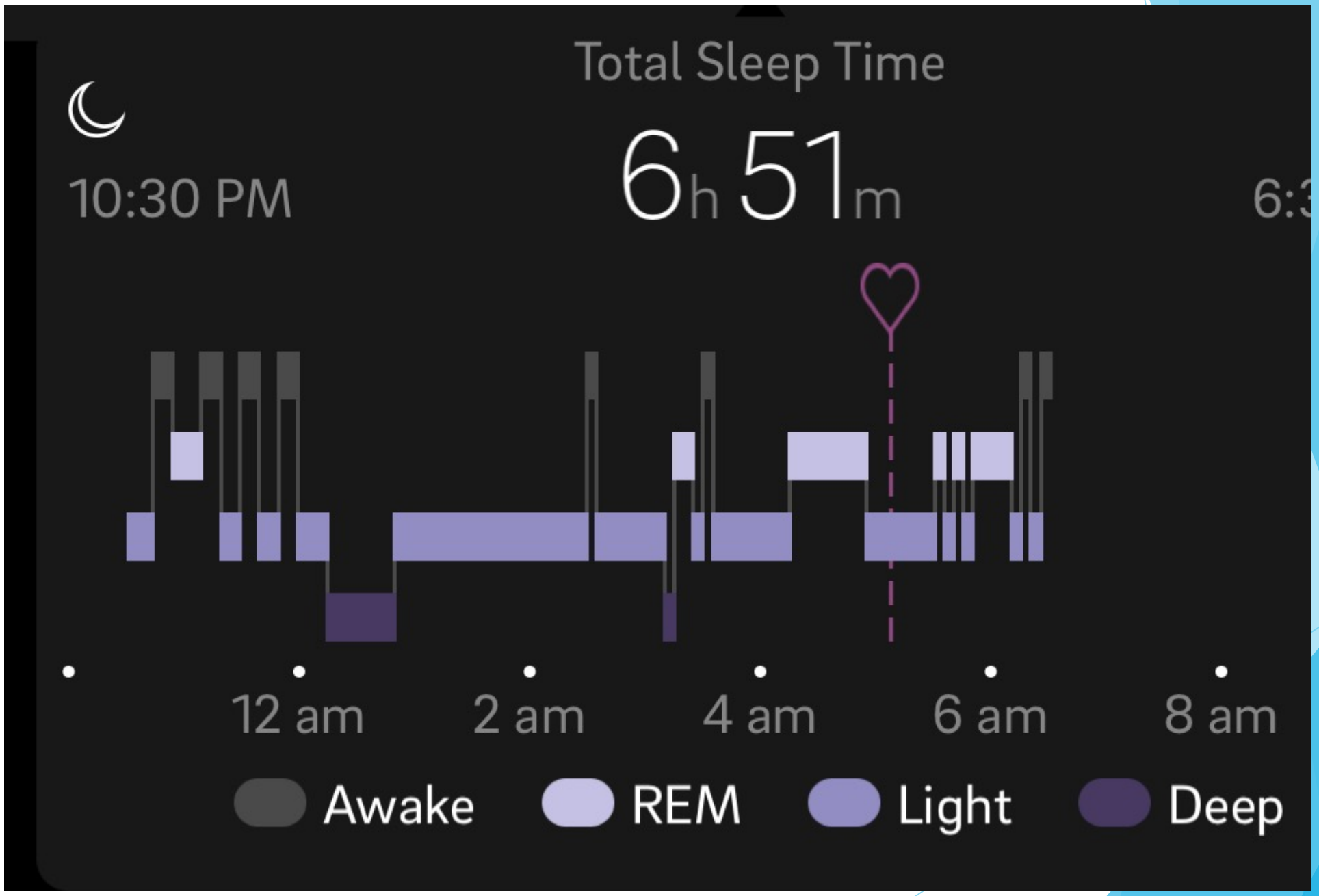
- Obese. Snores and gasps. High BP. Edema.
- Daytime somnolence not from medications
- Chronic opioids, benzodiazepines, polypharmacy
- Unexplained awakenings
- Widespread pain and stiffness
- Persistent sleep difficulties in spite of interventions.
- Worsening generally or lack of improvement over time on standard management of FM or ME/CFS

Observing/Monitoring sleep

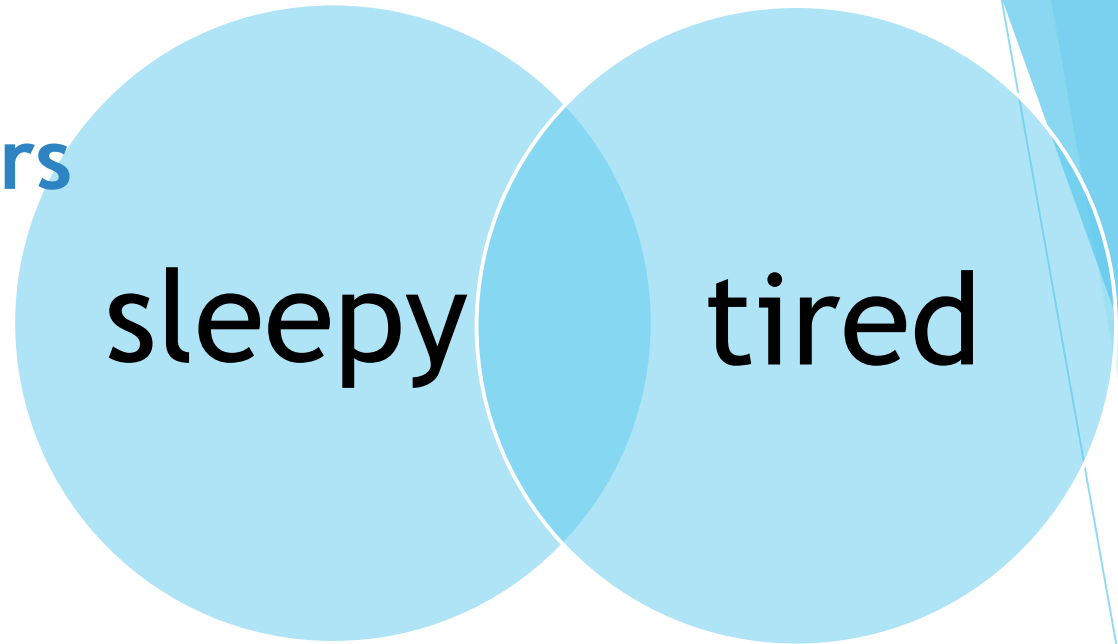
- **Polysomnography**---$$$ and good for some observations.
  - "Sleep lab artifact" can be high and is often ignored.
- **Home sleep study**---relatively new and lacks only the EEG leads
- **Pulsoximetry overnight**---only records when oxygen dips too low
- Patients should monitor their own sleep!
  - Fitbit or other self monitoring devices
  - Oura-ring (ouraring.com)

Last Week — 4 hr 58 min avg

Sat	11:44 PM – 9:45 AM	5 hr 46 min
Thu	11:47 PM – 10:08 AM	6 hr 31 min
4/6	11:50 PM – 7:21 AM	3 hr 50 min
4/5	12:40 AM – 8:48 AM	3 hr 44 min


Total Sleep Time
10:30 PM
6h 51m
6:3
12 am
2 am
4 am
6 am
8 am
Awake
REM
Light
Deep

Primary sleep disorders cause somnolence



Somnolence may be more treatable than fatigue:

- Sleep deprivation (all causes)
- Medications
- Illness (neurologic, endocrine, inflammation)

ESS (Epworth Sleepiness Scale) helps identify sleepiness vs fatigue

2. Central Sensitivity impact on sleep

- Pain amplification/hyperalgesia (FM)
  - Pain disrupts sleep and may contribute to alpha wave intrusion*
- All sensory amplification in ME/CFS and FM may impact sleep
  - Pain… Noise... Bright light... Temperature intolerance...
- Central “overload” PEM
  - Tired but wired
  - Too exhausted to sleep and “over-signaling”

*The significance, assessment, and management of nonrestorative sleep in fibromyalgia syndrome. Modofsky, H. CNS Spectrums 2008;13:22-6

Central Sensitivity

- Medications of interest: *[pregabalin is FDA approved BUT only for pain of FM otherwise all discussion is "off label"]*
  - gabapentin or pregabalin
  - low dose naltrexone (LDN)* thought to calm glial cell activation (1-5 mg)
  - low dose clonazepam 0.5 mg
  - amitriptyline, doxepin 5-20 mg
  - mirtazapine 7.5-15 mg
- Wind down. Quiet. Dark. Good temp. Ear plugs.
- Reduce activation (no bright screens)
- Prevent "crash over-signaling". "Pace" to prevent PEM.

*Younger, Jarred 2014

3. Autonomic Nervous System

- **Sympathetic** >> *parasympathetic**
  - Adrenalin/epinephrine and norepinephrine
  - Adrenal gland and adrenergic alpha and beta receptors via ANS
  - Increased HR (heart rate) and decreased HRV (heart rate variability) during sleep.
    - increased sympathetic tone
    - decreased vagal tone (parasympathetic tone)

Boneva 2007, Burton 2010

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

POTS and Orthostatic Intolerance (OI)

- The rapid heart rate response to orthostatic hypotension is a sympathetic nervous system response (fight or flight)
- Rapid heart rate can be compensatory, but there are also antibodies that act as adrenergic receptor agonists and antagonists
- Autoantibodies against alpha and beta receptors are found in post-viral POTS*
  - inhibit peripheral Alpha1R → vasodilation
  - Inhibit Beta1R → slows the heart rate
  - Stimulate Beta1R receptor → increase HR

Autoimmune Basis for Postural Tachycardia Syndrome.
Hongliang L…Kem DC. JAMA. Feb 26, 2014

Autonomic Nervous System

- If… **Sympathetic** > *parasympathetic*
- Change to: **Parasympathetic >** *Sympathetic*

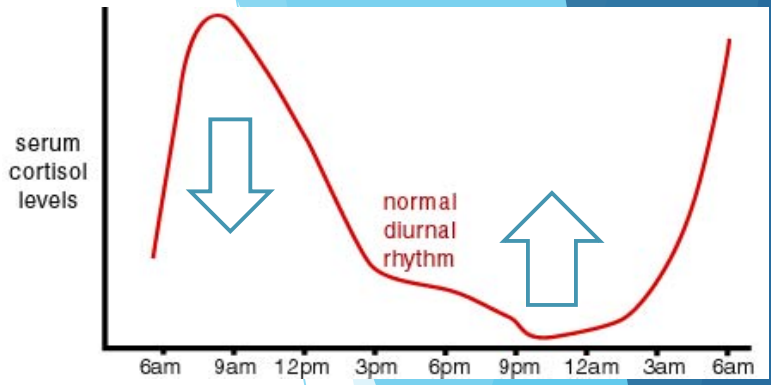
  Slow deep breathing and relaxation exercises.

  Take breaks from worries and stressors.

  Read a boring book before bed.

  Calming, not activating, activities
- Beta receptor blockade/inhibition or central alpha agonist:
  - propranolol 10-20 mg 2-3 hours before bed?
  - clonidine 0.1-0.2 mg at bed?

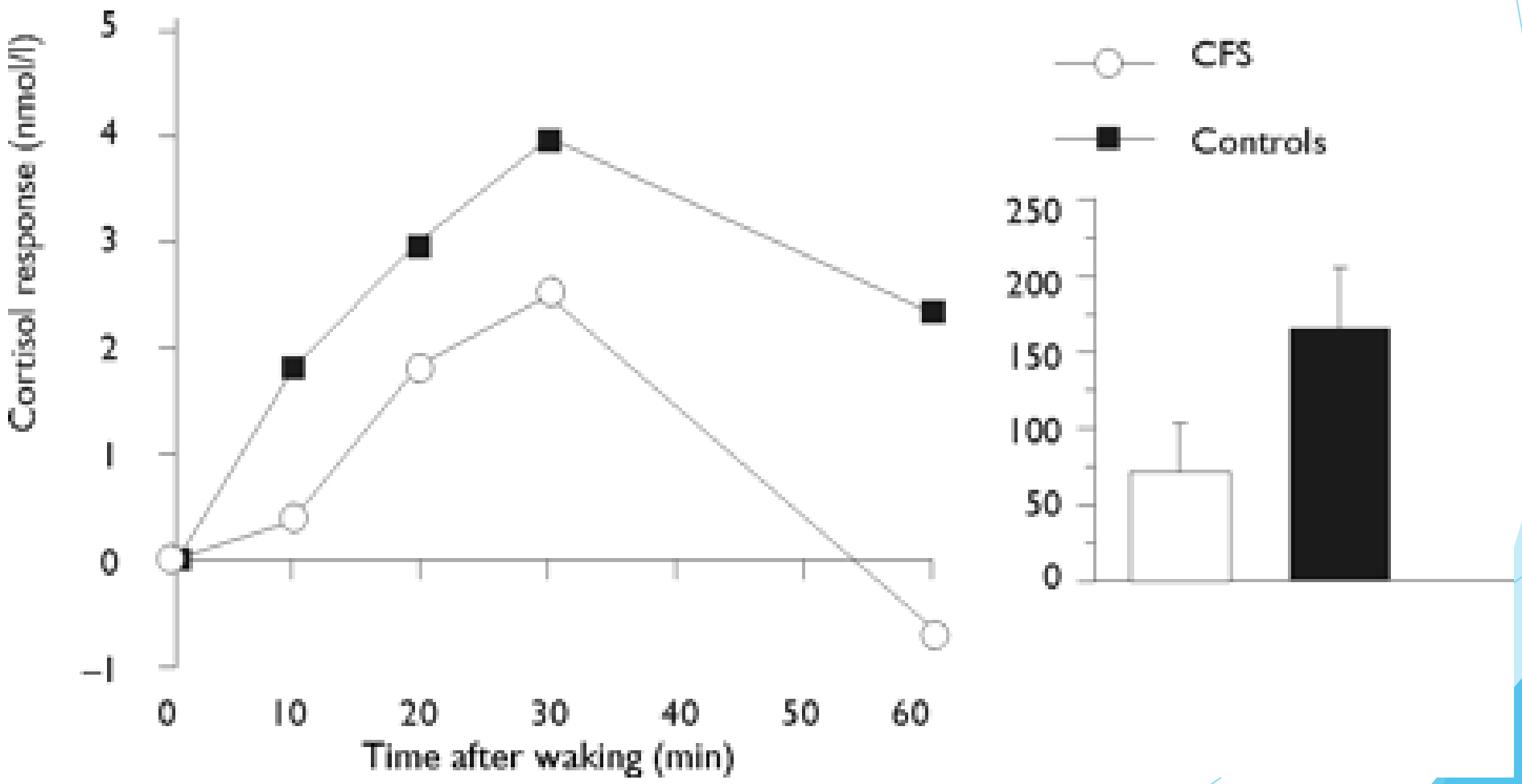
4. HPA-axis in ME/CFS



- Attenuated (reduced) AM cortisol level.
- Loss of normal circadian rhythm in terms of cortisol levels.
- Overall cortisol levels are lower than average (low normal)
- Adrenals and pituitary seem to work OK
- Hypothalamus →

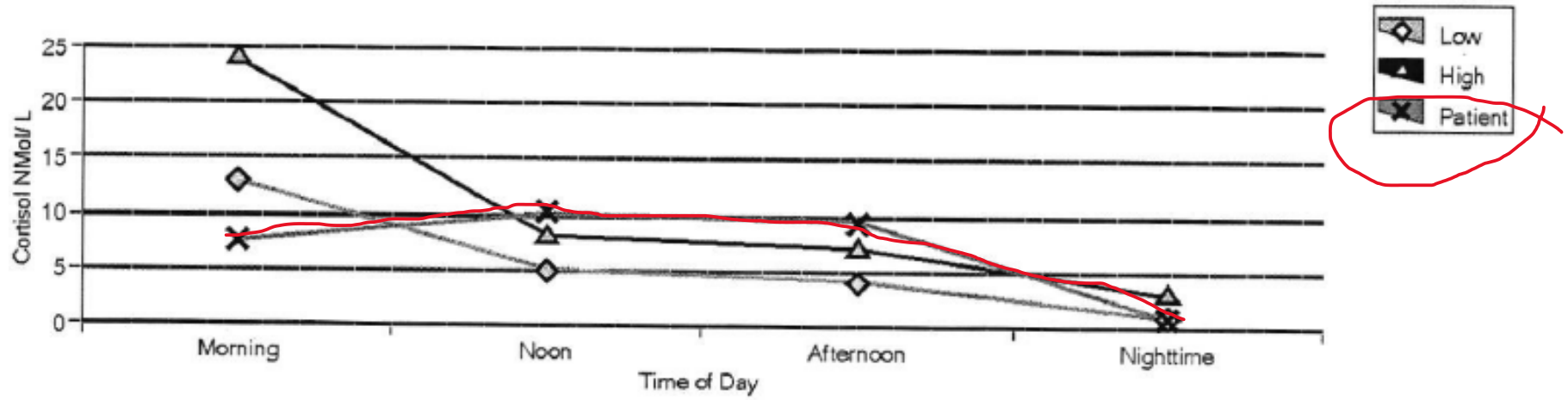
Salivary cortisol response to awakening in chronic fatigue syndrome. Roberts AD, et al. Br J Psychiatry 2004;184:136-41.
Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. Nater UM, et al. Psychosom Med 2008;70:298-305.

Salivary cortisol response to awakening in CFS. Roberts AD et al 2004.



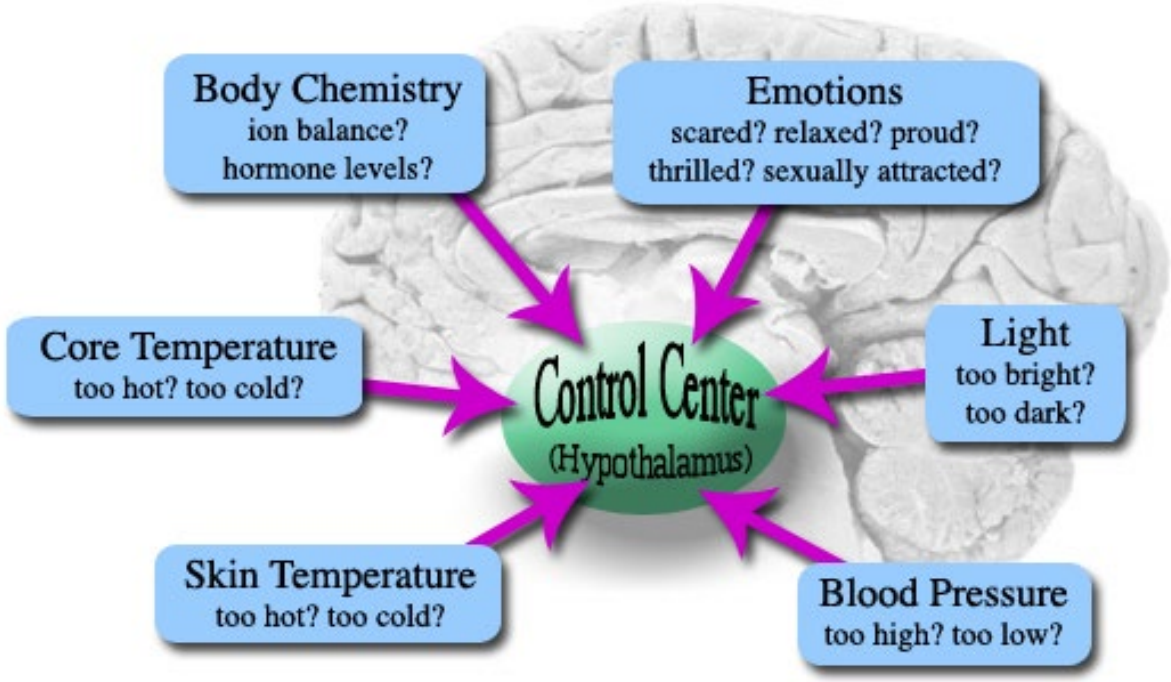
Functional Adrenal Stress Profile - 201

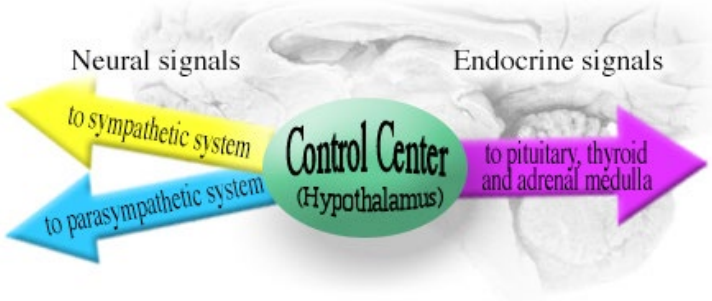
Parameter	Result	Reference Range	Units
Cortisol - Morning (6 - 8 AM)	**7.6***	13.0 - 24.0	nM/L
Cortisol - Noon (12 - 1 PM)	**10.4***	5.0 - 8.0	nM/L
Cortisol - Afternoon (4 - 5 PM)	**9.4***	4.0 - 7.0	nM/L
Cortisol - Nighttime (10 PM - 12 AM)	**0.9***	1.0 - 3.0	nM/L
Cortisol Sum	28.3	23.0 - 42.0	nM/L
DHEA-S Average	3.19	2.0 - 10.0	ng/mL
Cortisol/DHEA-S Ratio	**8.87***	5.0 - 6.0	Ratio



33 year old male with ME/CFS of 2 year duration

Hypothalamus…





Peripheral feedback to the hypothalamus:

Autonomic/Visceral
--blood pressure, volume, chemistry

Sensory Input and special senses
-- touch, sight, smell, hearing, taste, balance

Limbic System, Thalamus, and Cerebral Cortex
--pain and emotion

Hypothalamic Receptors
-- body temp
-- blood sugar and electrolyte concentrations
-- hormones from body and pituitary
-- GI signaling
--cytokines, fever causing substances

http://corposcindosis.blogspot.com/

Develop better sleep communication

- SLEEP 0 1 2 3 4 5 6 7 8 9 10
- MOOD 0 1 2 3 4 5 6 7 8 9 10
- PAIN 0 1 2 3 4 5 6 7 8 9 10
- HEADACHE 0 1 2 3 4 5 6 7 8 9 10
- FATIGUE 0 1 2 3 4 5 6 7 8 9 10
- FUNCTION 0 1 2 3 4 5 6 7 8 9 10

Sleep disruptions are varied

0123 Can’t go to sleep
0123 Restless sleep
0123 Wake up too early
0123 Can’t go back to sleep
0123 Need too much sleep
0123 Need to take naps
0123 Unrefreshing sleep
0123 Restless legs
0123 Leg cramps
0123 Myoclonic jerks (involuntary jerking of limbs)
0123 Snoring
0123 Stop breathing during sleep

0= none 1= infrequent 2= moderate in severity or frequency 3= severe or frequent

Sleep problems:

0 1 2 3	Can't go to sleep
0 1 2 3	Restless sleep
0 1 2 3	Wake up too early
0 1 2 3	Can't go back to sleep
0 1 2 3	Need too much sleep
0 1 2 3	Need to take naps
0 1 2 3	Unrefreshing sleep
0 1 2 3	Restless legs
0 1 2 3	Leg cramps
0 1 2 3	Myoclonic jerks (involuntary jerking)
0 1 2 3	Snoring
0 1 2 3	Stop breathing during sleep

Sleep problems:

0 1 2 3 Can't go to sleep
0 1 2 3 Restless sleep
0 1 2 3 Wake up too early
0 1 2 3 Can't go back to sleep
0 1 2 3 Need too much sleep
0 1 2 3 Need to take naps
0 1 2 3 Unrefreshing sleep
0 1 2 3 Restless legs
0 1 2 3 Leg cramps
0 1 2 3 Myoclonic jerks (involuntary jerking)
0 1 2 3 Snoring
0 1 2 3 Stop breathing during sleep

Sleep problems:

0 1 **2** 3	Can't go to sleep
0 1 **2** **3**	Restless sleep
0 1 2 3	Wake up too early
0 1 **2** 3	Can't go back to sleep
0 **1** 2 3	Need too much sleep
0 **1** 2 3	Need to take naps
0 1 2 **3**	Unrefreshing sleep
0 1 **2** **3**	Restless legs
0 1 **2** 3	Leg cramps
0 1 **2** 3	Myoclonic jerks (involuntary jerking)
0 **1** 2 3	Snoring
0 1 2 3	Stop breathing during sleep

Treatable comorbid conditions may contribute to fatigue and sleep disturbances

- Primary sleep disorders
  - Obstructive sleep apnea, airway resistance
  - Central sleep apnea
  - Movement disorders (RLS, myoclonus)
  - Narcolepsy (MSLT on no medications)
- Pain disorders
- Mental health conditions
- Urinary frequency disorders
- Snoring spouse, active pets, etc…

Medications may disrupt sleep or contribute to primary sleep disorders

- Caffeine, stimulants
- Decongestants (pseudoephedrine)
- Antidepressants (bupropion, fluoxetine, sertraline…)
- Opioids
- Benzodiazepines
- Drugs that increase dopamine (inhibits melatonin release)
- polypharmacy

Additional Recommendations:

- Improve sleep hygiene (routine timing, environment).
- Daytime activity. Get physically tired---but not exhausted, “wound up” or relapsing (PEM).
- Be wary of long or late naps.
- Minimize sedating drugs during the day.
- Aim at all the CAUSES of sleep disruption vs “drugged” to sleep
- Simplify use of medications and use them skillfully
  - Sleep onset? ...wind down, establish cycles, short acting drugs, earlier dosing of longer acting sedating medications
  - Light sleep and frequent awakening? …reduce interruptions, low dose longer acting meds
  - Early morning awakening? …med rebound or withdrawal? Too much sleep? Depression?

Drugs often used for sleep disturbances:

Longer acting sleep "sustainers" *--off-label use for sleep--*

***TCA:** amitriptyline (10-20 mg), doxepin (5-20 mg)

Other antidepressants: trazodone 25-100 mg, mirtazapine 7.5-15 mg

***Anticonvulsants:** gabapentin 300-1200 mg, topiramate 25-100 mg

Benzodiazepines: clonazepam or lorazepam 0.5-1 mg

Atypical antipsychotics: quetiapine 12.5-50 mg, olanzapine 2.5-5 mg

These longer acting drugs may cause "hangover" symptoms the next morning if dosed too high or taken too late in the evening, along with unwanted weight gain or worsen orthostatic intolerance.

Choose a sleep medication based on comorbid conditions and the nature of the sleep disturbances.

*additional benefits for pain

Drus often used for sleep disturbances:

Sleep "initiators" or hypnotics

FDA approved for insomnia, not specifically for fibromyalgia or ME/CFS

zolpidem 5-10 mg (approx 4 hours, CR 6 hours)

zaleplon 5-10 mg (approx 2 hour duration)

eszopiclone 1,2 or 3 mg (approx 6 hour duration)

benzodiazepines, ex: *temazepam* 15-30 mg (tolerance/habituation)

- *Chronic use discouraged, and thus problematic for chronic illness*
- *Tolerance or dependence and rebound insomnia typically develops.*
- *Better for sleep initiation than to sustain sleep all night.*
- *Better for PRN use rather than nightly use*

Drugs for sleep disturbances:

Belsomra/suvorexant: an orexin receptor antagonist (suppresses wakefulness)

May be in a class of it's own.

Natural sleep (drug free) is best,
but chronically disrupted or inadequate sleep
of FM and ME/CFS may be insidiously harmful as well.

There is no perfect medication for sleep.
Almost all have some adverse effects.

Use drugs skillfully.

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Don't give up because
achieving restorative sleep
is a constant battle.
More restorative sleep improves
fatigue, cognition, pain and mood.