

Fatigue in Progressive Multiple Sclerosis



Heidi Maloni PhD, ANP-BC, CNRN, MSCN
heidi.maloni@va.gov

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• 1

Case: J.Z. EDSS: 6.0

- Symptom: Overwhelming fatigue
 - Impacts his ability to think
 - Impacts his ability to complete tasks
 - Impacts his ability to get a job
 - Impacts decision-making; refuses gait aides
 - Too tired to pay attention; forgets food on stove
- Symptom: Poor sleep; mood irregularities
 - Never feels rested
 - Often does not get dressed
 - Isolates from friends and family
 - Sleepy and gets lost driving
 - Up to void 4x/night
 - Poor appetite; weight loss

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• 2

Fatigue Defined

“a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”

Pathological exhaustion affecting social, physical and occupational well-being

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• 3

MS Fatigue Described

- Occurs in 80% and deemed the most disabling symptom (40%) and worst symptom (55%)
- Occurs daily even after a good nights sleep
- Worsens as the day progresses
- Comes on suddenly
- Heat and humidity aggravate
- Associated physical, emotional and mental exhaustion
- More likely to interfere with daily responsibilities
- Responsible for work place flight

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• 4

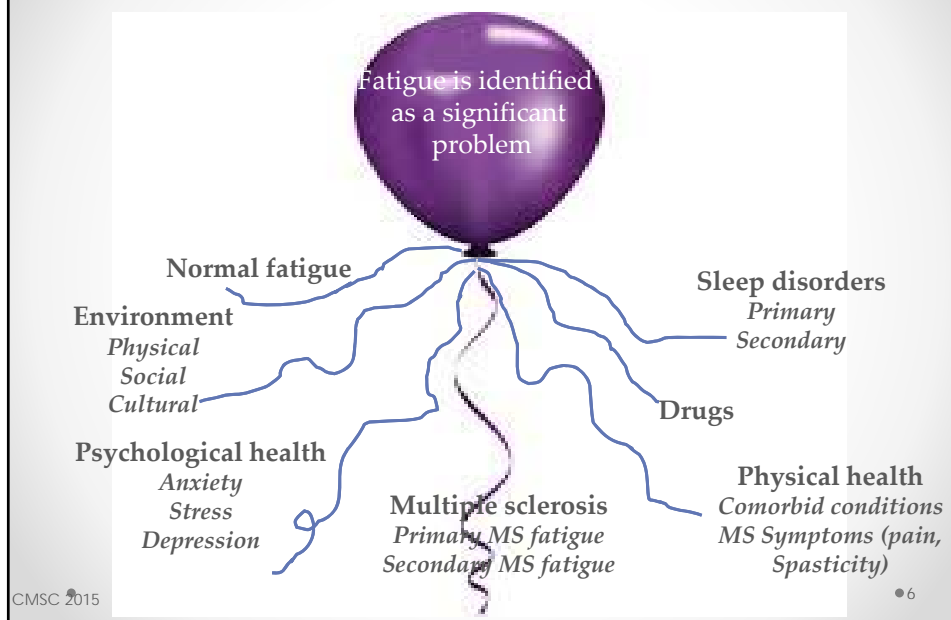
Fatigue: Patient's View

- "I take a shower in the middle of the day and I don't know if I should dress or put on clean pajamas"
- "I'm exhausted to the bone. I can't get out of my own way"
- "I feel like I am moving underwater 24/7"
- "Lifting a fork feels like a 10 pound weight"
- "I fall asleep watching my favorite TV shows"
- "My family thinks I'm faking and trying to get out of doing stuff. They accuse me of being lazy"

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• 5

The Mixed Balloon of MS Fatigue



Primary Fatigue

Direct result of damage within the CNS

- Proinflammatory cytokines
 - Caused by ongoing inflammation
 - Increased expression of IL-6, INF γ and TNF α correlates with fatigue severity
- Endocrine influences
 - May relate to low serum levels of DHEA and DHEAS
- Axonal loss
 - MRS studies of decreased NAA/Cr ratios suggesting axonal loss in progressive MS
 - Brain atrophy (basal ganglia and prefrontal cortex) contributes to cognitive fatigue

• CMSC 2015 Heesen et al, 2006 J NeuroNeurosurg Psychiatry; Tellez, 2006, MS; Tellez et al, 2008, Neuroradiology; Pardini 2010; Tartaglia et al, 2008, Arch of Neur; Marrie, 2005, J Neurol Sci • 7

Primary Fatigue

- Altered patterns of cerebral activation
 - Decrease in glucose in prefrontal cortex and basal ganglia by PET
 - Compensatory reorganization and increased brain recruitment seen on fMRI
 - Impairment of volitional drive of descending pathways due to involvement of motor afferent pathways involving motor cortex

• CMSC 2015 Leocani et al, 2008 Neurol Sci • 8

Secondary Fatigue

- Arising from associated conditions or accumulation of disease burden
 - Poor sleep: nocturia; sleep apnea; restless legs
 - Weakness or deconditioning
 - Other medical issues (anemia, infection, heart & thyroid dz.)
 - Mood: depression; anxiety
 - Medication side effects
 - Heat sensitivity
 - Poor nutrition
 - Other MS symptoms: spasticity; pain; neurogenic bladder

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• 9

Secondary Fatigue

- Study of 2469 subjects supports strong and significant associations between clinically significant fatigue and modifiable lifestyle factors¹
 - Fatigue is associated with obesity, DMT use, poor diet
 - reduced odds of fatigue with exercise, fish consumption, moderate alcohol use, and supplementation with vitamin D and flaxseed oil.
- Sleep²
 - sleep disturbance was the greatest predictor of fatigue in MS
 - individuals with MS are three times more likely to experience sleep difficulties than controls
 - bladder incontinence as the greatest contributor to disturbed sleep, followed by muscle stiffness and leg spasms, in more than 50% of patients

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1. [Weiland, et al. \(2015\). Plos One. 18:10\(2\) 5541.](#)
 2. [Strober \(2015\). Frontiers in Neurology. 21\(6\)](#)

• 10

Sleep Management

- Effective treatment of sleep problems result in reduction of self-reported fatigue and sleepiness
- Treatment options:
 - Sleep hygiene
 - CPAP
 - Pramipexole for RLS
 - Clonazepam for REM behavior disorder sleep
 - CBT for insomnia
 - Muscle relaxation

Strober (2015). *Frontiers in Neurology*, 21(6)

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• 11

Fatigue in Progressive MS

- EDSS correlates with fatigue scores
- More severe fatigue reported in progressive MS
- Fatigue is related to brain atrophy
- Related to impaired quality of life independent of disability
- Higher working load required of brain to perform usual physical and mental activities
- No significant correlation between MS fatigue, age, sex, disease duration

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Patrick et al, (2009) NY State MS Consortium Database. MS

• 12

Progressive MS

Respiratory Muscle Weakness and Fatigue

- Respiratory muscle performance is correlated with perceived fatigue (MFIS)
- Expiratory muscle strength was correlated with self-reported physical fatigue
- Respiratory endurance correlated to reductions in physical function and sleep quality
- PT important to proper seating; breathing exercises

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[Ray, Mahoney, Fischer, Disabil Rehabil. 2015 Apr 8;1-6. \[Epub ahead of print\]](#)

[Measures of respiratory function correlate with fatigue in ambulatory persons with multiple sclerosis.](#) • 13

Management of Fatigue

- Assessment
 - Assess primary and secondary fatigue
 - Most discriminating scales¹
 - Fatigue Impact Scale²
 - Fatigue Severity Scale³
- Intervention
 - Drug management
 - Nondrug management
 - Exercise
 - Energy conservation education



1. Flachenecker et al (2002). MS

2. Krupp et al., Arch of Neurology, 1989; 46, 1121-1123.

3. Fisk JD, et al. 1994. Can J of Neuro Sci; 21: 9-14

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• 14

Case: J.Z.

- Assessment
 - Symptoms of primary fatigue in progressive disease
 - Neurological exam: EDSS 6.0
 - MRI: Multiple periventricular T2 lesions and brain atrophy
 - Mean FSS score 5 (indicating severe fatigue)
 - Symptoms of secondary fatigue identified
 - Positive Patient Health Questionnaire (OHQ-2)
 - Little interest or pleasure in doing things
 - Feeling down, depressed or hopeless
 - Neurocognitive testing indicating deficits in attention and noting comorbid fatigue and depression
 - Diagnosed neurogenic bladder with failure to empty
 - Poor scores on MND-SWS and MSQOL-54
 - Resistant to medication intervention and use of gait aide

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• 15

Fatigue Severity Scale

During the past week, I have found that:

1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

rate each item from 1 (strongly disagree) to 7 (strongly agree). FSS Score = mean rating across all 9 questions - i.e., 1 → 7. Higher score = worse fatigue.

FSS mean score >4 indicates severe fatigue

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• 16

Krupp et al., Arch of Neurology, 1989; 46, 1121-1123.

Modified Fatigue Impact Scale

Twenty-one question scale of fatigue in past 4 week.
Never (0), Rarely (1), Sometimes (2), Often (3), Almost always (4).

- I have been less alert
- I have had difficulty paying attention for long periods of time
- I have been unable to think clearly
- I have been clumsy and uncoordinated
- I have been forgetful
- I have had to pace myself in my physical activities
- I have been less motivated to do anything that requires effort
- I have been less motivated to participate in social activities
- I have been limited in my ability to do things away from home
- I have had trouble maintaining physical effort for long periods

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• 17

MFIS continued

- I have had difficulty making decisions
- I have been less motivated to do anything that requires thinking
- My muscles have felt weak
- I have been physically uncomfortable
- I have had trouble finishing tasks that require thinking
- I have had difficulty organizing my thoughts when doing things at home or at work
- I have been less able to complete tasks that require physical effort
- My thinking has been slowed down
- I have had trouble concentrating
- I have limited my physical activities
- I have needed to rest more often or for longer periods

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Fisk JD, et al. 1994. Can J of Neurol Sci; 21: 9-14

• 18

Pharmacologic Management of Fatigue

Drug	Dose	Adverse Event
Modafinil	up to 400 mg/d	Headache Anxiety
Armodafinil	150 to 250 mg/d	Nausea Rhinitis Insomnia Diarrhea Palpitations
Amandadine	100-200mg daily	Hallucinations Lightheadedness Peripheral edema Nausea Insomnia Constipation Livedo reticularis

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Pharmacologic Management of Fatigue

Drug	Dose	Adverse Event
Methylphenidate	10-60mg/d	Insomnia Decreased appetite
Concerta ER	18-72mg/d	HTN Tachycardia
Dexmethylphenidate IR, ER	2.5, 5, 10 bid	Nausea Constipation
Amphetamines: Dextroamphetamines Methamphetamine Adderall, Adderall XR Lidexamfetamine	5-60mg/d 20-25mg/d 5-40mg/d 20-70mg/d	Insomnia Feeling faint Nausea Constipation HTN Tachycardia

Pharmacologic Management of Fatigue

Drug	Dose	Adverse Event
Bupropion	150-450mg/d	Anxiety Insomnia Weight loss Agitation Headache Constipation
Fluoxetine (stimulates energy metabolism enhancing glyconeogenesis)	10-40mg/d	Nausea Headache Insomnia Nervousness Anorexia Diarrhea Dizziness

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● 21

Non Drug Management

- Address secondary causes
- Rehabilitation interventions
 - Evaluation of gait and safety
 - Exercise
 - ergonomics
- Environment
 - Cooling
 - Energy conservation techniques
- Education
 - Pacing
 - Stress management
 - Body mechanics



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Mathiowetz et al, 2005 MS (11), 592-601
Asano & Finlayson, 2014. MS Inter

● 22

Case: J.Z.

- Intervention in fatigue management
 - Use of multidisciplinary team: physical and occupational therapy, mental health, dietitian, urology, sleep clinic, social work, nursing; community services-NMSS, neuropsychologist
 - Appropriate rest and activity ratio
 - PT encourage assistive device to conserve energy
 - Involve in exercise class
 - Involve in NMSS class, "Free From Falls"
 - Support group

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• 23

Case J.Z.

Management of Secondary Fatigue

- Management of any symptoms that may require excessive energy expenditure needed for ADLs
 - PT for assistive devices
 - OT in home safety eval and home care management strategies (cooking; timers; alarms)
- Cognition
 - Driver rehab; GPS; vocational rehab
- Bladder
 - Behavior management
 - Urology support
 - Medication HS
- Sleep
 - Hygiene
 - Mindfulness tapes
- Depression
 - Counseling and support group
 - Medication

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• 24

Environmental Management

- Energy conservation to make activities more energy-efficient
 - Stress management and life balance
 - Timed rest-power naps
- Heat management: cooling strategies to avoid the fatigue caused by elevations in core body temperature due to heat, exercise-related exertion, and fever
- Regular aerobic exercise, geared to the person's ability, to promote cardiovascular health, strength, improved mood, and reduce fatigue

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● 25

Education

- Education about energy effectiveness strategies - defined as "the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home, and leisure activities"¹
 - Appropriate rest to activity ratio
 - Use of assistive devices
 - Examining standards and priorities
 - Delegating and organizing
- Energy conservation course decreased the impact of fatigue and enhance QOL²

1. Multiple Sclerosis Council for Clinical Practice Guidelines, PVA 1998

2. Mathiowetz et al, Multiple Sclerosis, 2005, 11

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● 26

Studies of Exercise and Fatigue

- MS fatigue management rehabilitation interventions (both exercise and educational interventions) appear to have a stronger and more significant effect on reducing the impact or severity of patient-reported fatigue compared to the two most commonly prescribed fatigue medications¹
- Aquatic exercise can improve the QoL and decrease fatigue severity and fatigue perception²
- Gene expressed interferon response to exercise³
- Body weight support treadmill⁴
- Aerobic training feasible in progressive MS⁵

1. Asano & Finlayson. (2014). Multiple Sclerosis International
2. Kooshair et al. (2014). J of Sports Med & Phy Fitness
3. Mulero et al (2015). J Neuroimmunolgy
4. Pilutti (2013). Apl Physio Nutr Metab
5. Briken et al (2014) Multiple Sclerosis

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• 27

Exercise in Progressive MS

- Few studies of exercise on fatigue in progressive MS
- Aerobic exercise improves fatigue
- Anecdotal use
 - Seated exercises
 - Aerobic-stationary bike
 - inspiratory muscle exercise
 - Vestibular rehabilitation
 - Progressive resistance training
 - Yoga

Morrison & Stuifbergen, 2014. J Neuroscience nsg 46(3). 171-179.
Feinstein. 2014. Multiple Sclerosis 20(3) 269-70

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• 28

J.Z.

Activity Diary

- What is important
- Prioritize the day
- Set goals and priorities
- Track the day and fatigue levels
- Understand the relationship between activities and symptoms
- Identify problems
- Clues to change

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● 29

Activity Diary

Date _____ Describe last nights sleep __ (1 to 10) __

Time	F	V	S	Activity	Comment (symptoms)
6:00 AM					
7:00 AM					
8:00 AM					
9:00AM					
10:00 AM					
11:00 AM					
12 Noon					
1:00 PM					
2:00 PM					
3:00 PM					
4:00 PM					
5:00 PM					
6:00 PM					
7:00 PM					
8:00 PM					
9:00 PM					
10:00 PM					
11:00 PM					

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● 30

J.Z. Add Exercise

- 25-30 minutes; three to four times a week
 - Aerobic: work up gradually; strive for moderate intensity
 - Strengthening: 10-15 reps; two sets for upper and lower body
- Structured, endurance exercise program
 - Gentle stretching exercises
 - Strengthening exercises
 - Low impact aerobic exercises
 - Pool exercises
 - Yoga
 - Adapted tai chi
- Over exercise will cause fatigue

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• 31

J.Z. Attention to Nutrition

- Refer to dietitian
- Several small meals low in fat and sugar
- Eat as soon as you wake up
- Create a power pantry of foods
- Stock up with precut, premeasured foods
- Consider a delivery service- Blue Apron, Giant's Peapod & Safeway
- Community pantry

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• 32

Case: J.Z.

- Adopted
 - Yoga and mindfulness workshop
 - Rowing team
 - Cane
 - Cooling vest
 - Computer CBT course
 - Support group
 - Volunteer summer parks rec program
 - Medications
 - Concerta
 - Desmopressin HS(resistant to IC)
 - Fluoxetine

○ **Fatigue requires multidisciplinary team management and self-efficacy for goal directed behaviors**

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● 33



Thank You

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● 34