

Why am I so tired? An Overview of Chronic Fatigue Syndrome

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Objectives

- Define chronic fatigue syndrome
- Discuss the signs and symptoms of chronic fatigue syndrome
- Analyze the differential diagnosis of chronic fatigue syndrome

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Case History

- 37 yo female
- Internet technologist at a bank
- Active in sports, works out, maintains household, slept well at night
- Developed flu-like illness
 - Bed bound & slow to recover
- Within days noticed unusual fatigue after minimal activity

Unger, E. R., et al., (2016). CDC grand rounds: Chronic fatigue syndrome – Advancing research and clinical education. *Morbidity and Mortality Weekly Report*, 65(50 & 51).

Case History

- Other symptoms soon followed:
 - Insomnia
 - Joint pain
 - Muscle pain
 - Weakness
- Difficult recalling recent conversations & events
- Difficulty concentrating & comprehending reading or TV shows

Unger, E. R., et al., (2016). CDC grand rounds: Chronic fatigue syndrome – Advancing research and clinical education. *Morbidity and Mortality Weekly Report*, 65(50 & 51).

Case History

- Easily lost train of thought & friends had to finish her sentences
- Restless at night
- In mornings:
 - Unrefreshed (even with 9 hrs sleep)
 - Body stiff & sore
 - Felt foggy

Unger, E. R., et al., (2016). CDC grand rounds: Chronic fatigue syndrome – Advancing research and clinical education. *Morbidity and Mortality Weekly Report*, 65(50 & 51).

Case History

- Felt lightheaded when getting up quickly
 - Occasionally “saw stars”
- Attempted to keep up at home → exertion made symptoms worse & would get sick and chair-bound for 1-2 days afterward
 - Rely on friends & family to help

Unger, E. R., et al., (2016). CDC grand rounds: Chronic fatigue syndrome – Advancing research and clinical education. *Morbidity and Mortality Weekly Report*, 65(50 & 51).

Case History

- Evaluation by family physician:
 - Low BP (no immediate orthostatic BP drop)
 - Otherwise examination unremarkable
 - Laboratory tests unremarkable
- No explanation for symptoms → Patient became anxious, frustrated, & discouraged

Unger, E. R., et al., (2016). CDC grand rounds: Chronic fatigue syndrome – Advancing research and clinical education. *Morbidity and Mortality Weekly Report*, 65(50), 511.

CHRONIC FATIGUE SYNDROME

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Chronic Fatigue Syndrome

- Initially called chronic EBV syndrome
- Changed in late 1980s
 - Persistent fatigue not observed in EBV
- Fatigue is unique – not typical fatigue commonly experienced by everyone at some time

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CFS also called:

Myalgic encephalomyelitis (ME)

Chronic fatigue immune dysfunction

Systemic exertion intolerance disease

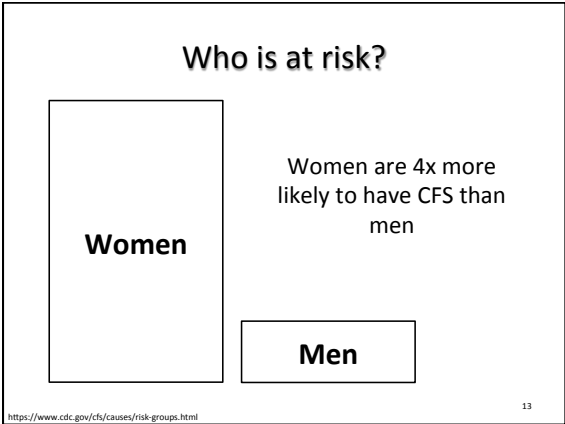
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Often results in significant reduction in activities



An estimated **1-4 million** adults in the US have
Chronic Fatigue Syndrome





Who is at risk?

Most often diagnosed in people ages 40-60 yr old

However...CFS may occur at any age

<https://www.cdc.gov/cfs/causes/risk-groups.html> 14

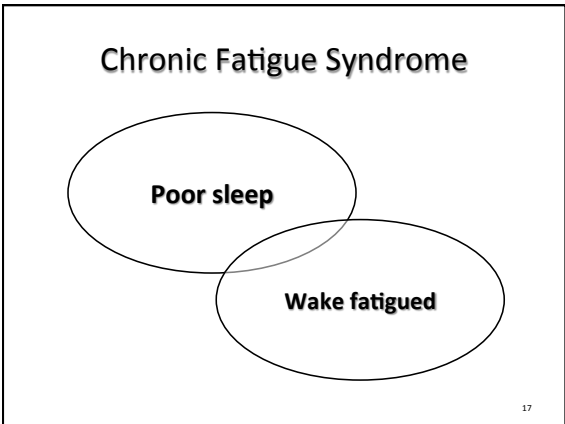


Is there a genetic link?

Observed in members of same family

Further research needed

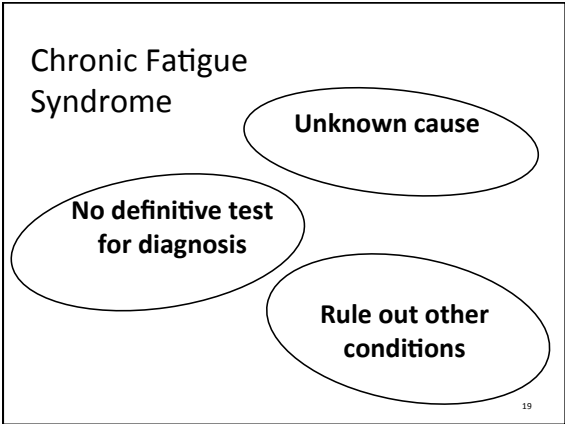
<https://www.cdc.gov/cfs/causes/risk-groups.html> 16



Severity of CFS similar to:

- Multiple sclerosis
- Lupus
- Rheumatoid arthritis
- Heart disease
- End-stage renal disease
- COPD
- Other chronic conditions

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- ### Possible Triggers of CFS
- Infection
 - Immune dysfunction
 - Hypotension
 - Nutritional deficiency
 - Stress that activates the HPA axis (hypothalamus, pituitary, & adrenal glands)

- ### Infections studied to determine if they trigger CFS:
- Epstein-Barr virus
 - Human herpesvirus 6
 - Enterovirus
 - Rubella
 - *Candida albicans*
 - Bornavirus
 - Mycoplasma
 - Ross River virus
 - *Coxiella burnetii*
 - Human retroviruses (HIV)

- ### Current research:
- Molecular testing from CFS patients looking for previous unknown infection (pathogen discovery)
 - EBV, Ross River virus, & *C.burnetii* → led to condition meeting CFS criteria in 10-12% cases
 - More severe symptoms with infection more likely to develop CGS symptoms
- No association between CFS & infection**
- <https://www.cdc.gov/cfs/causes/index.html>

- ### Can a change in immune status lead to CFS?
- Mixed findings
 - Hypothesis: stress or viral infection result in chronic cytokine production → leads to CFS
 - Auto-Ab & immune complexes observed in some CFS patients
 - No tissue damage

- ### Can a change in immune status lead to CFS?
- Some researchers found different T-cell activation markers in CFS patients than healthy persons
 - Inconsistent findings
 - Allergies could be predisposing factor
 - Not all CFS patients have allergies
 - However...many CFS patients report sensitivities (intolerances) to certain substances




Neurally Mediated Hypotension (NMH)

- Abnormally low BP & lightheadedness
- Disturbance in BP and pulse regulation observed in CFS
 - Lay patient on table, tilt to 70° for 45 min → monitor BP and HR
 - NMH or POTS → low BP, lightheaded, visual dimming, rapid HR

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Neurally Mediated Hypotension (NMH)




CFS patients experience light headedness or fatigue after standing for long period (especially in warm places) → this will trigger NMH or POTS

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Nutritional deficiency

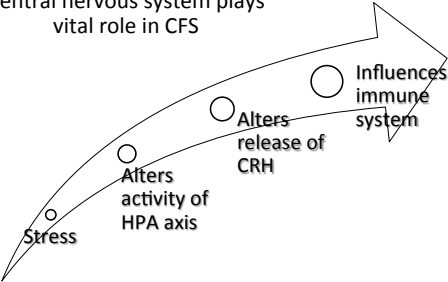
- Currently, no evidence to indicate that CFS is caused by nutritional deficiency
- Healthy, well-balanced diet should benefit any patient with chronic illness



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Hypothalamic-Pituitary Adrenal (HPA) Axis

Central nervous system plays vital role in CFS



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Hypothalamic-Pituitary Adrenal (HPA) Axis

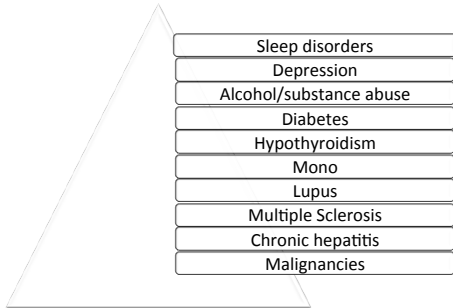
- Lower cortisol levels observed in some CFS patients
 - Still within RR, so can't be used for diagnosis
- Similar hormonal findings in fibromyalgia

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Chronic Fatigue Syndrome is often overlooked or misdiagnosed because symptoms are similar to many other illnesses

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Illnesses that resemble CFS



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Other diagnostic challenges

- Lack of a specific lab test or biomarker
- Sometimes, not obvious that a patient is ill
- Pattern on remission & relapse
- Variety of symptoms & severity

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Diagnosis of CFS

Patient history

Physical exam

Mental status

Lab tests

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Recommended Laboratory Screening Tests

- CBC
- Protein
- Albumin
- Glucose
- CRP
- Calcium
- Phosphorus
- Electrolytes
- ANA
- Rheumatoid factor
- Alkaline Phosphatase
- ALT & AST
- TSH & FT4
- Urinalysis
- Creatinine
- BUN

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3 Criteria for Diagnosis

1. Unexplained, persistent fatigue >6 mos.
2. Fatigue significantly interferes with daily activities & work
3. 4 or more of the following symptoms present for at least >6 mos:
 - Impaired memory or concentration
 - Postexertional malaise
 - Tender cervical or axillary lymph nodes
 - Unrefreshing sleep
 - Frequent sore throat - Headaches
 - Muscle pain - Joint pain

*Based on the International CFS Case Definition (1994), as recognized by the CDC

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Other Symptoms

Abdominal pain/bloating

Depression

Chills/night sweats

Visual disturbances

Dizziness

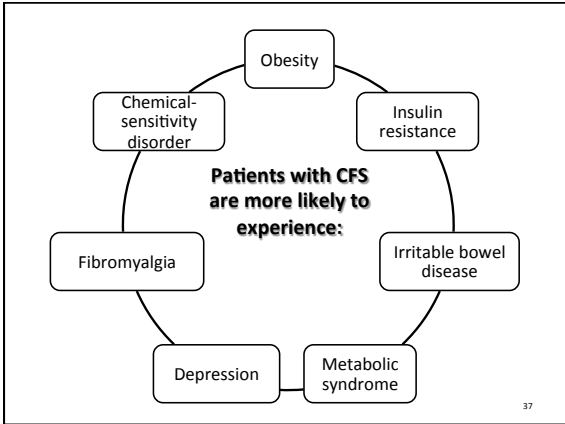
Balance problems

Fainting

Difficulty maintain upright position

Nausea

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What if a patient does NOT fit all of the criteria?

Patient may present with chronic fatigue, but does not have at least 4 of the 8 symptoms

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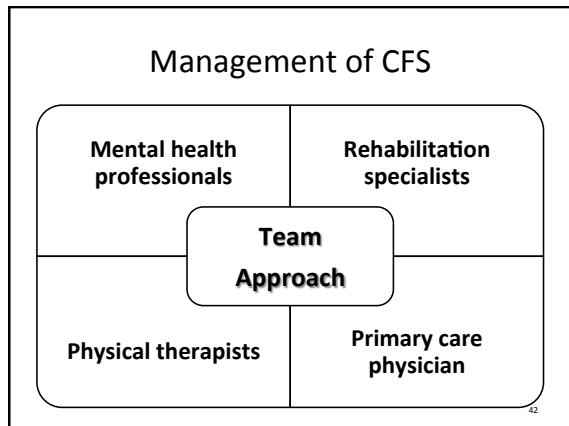
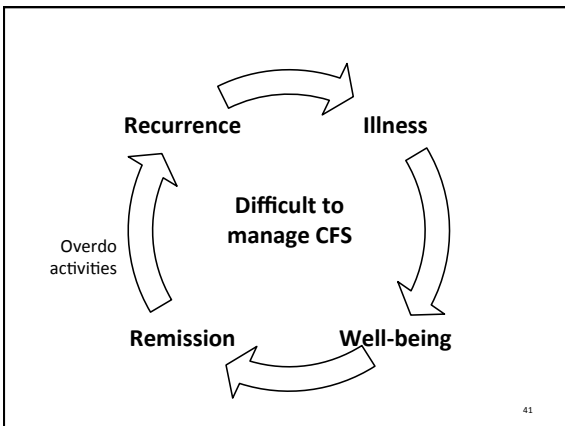
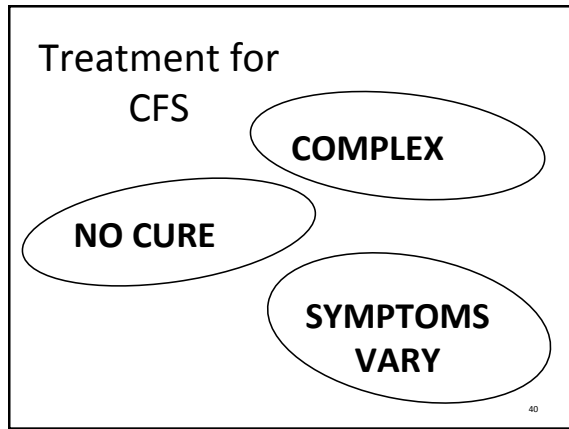
Idiopathic fatigue

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The woman presented at the beginning reveals many of the signs & symptoms experienced by patients with CFS

Important for physicians to recognize these and treat appropriately

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Rationale for Management

- Treat other conditions occurring at same time
- Identify most bothersome symptoms
- Medications to relieve symptoms
- Empower patient to be active in managing CFS

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Drug Therapy

- Few medications as possible
 - Small dose to start
- Consult clinician before any OTC medications/supplements
- Treat clinical depression only
- Multivitamins
- Avoid: narcotics for pain, sleep medication, herbal remedies

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Non-drug Therapy

Increase energy & decrease pain:

- Acupuncture
- Massage
- Deep breathing
- Relaxation therapy
- Yoga
- Tai-chi
- Stretching or light exercise before bed
- Cope with memory difficulties:
 - Use of organizer or scheduler
 - Puzzles
 - Word games

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Emotional issues with CFS

- Problems coping with unpredictable symptoms
- Uncertainty about future
- Feelings of guilt, loneliness, anxiety

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CFS can be life altering

- Loss of independence & financial security
- Changes in relationships
- Impact on school/work performance as result of memory or concentration problems

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Coping Strategies for CFS

Strengthen coping skills with emotional & psychological issues:

Counselor

Support groups

Employment

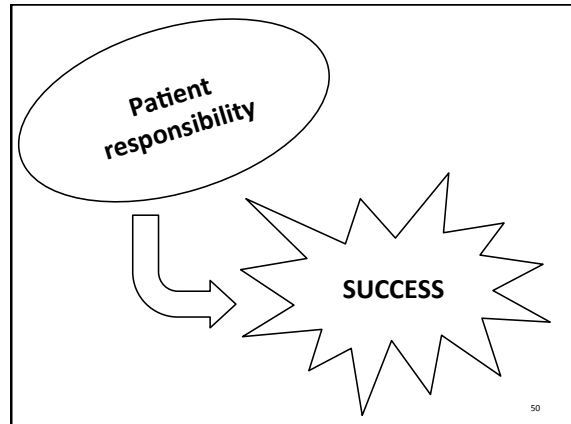
Impacts entire family → family education/counseling may be helpful

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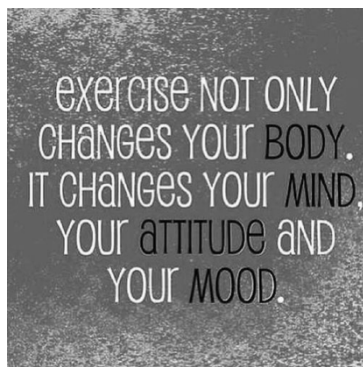
Cognitive Behavioral Therapy (CBT)

- Therapy for chronically ill patients
- Individualized & tailored to patient's needs
- Effective for CFS
 - Aware of stressors that worsen symptoms
- Often combined with exercise

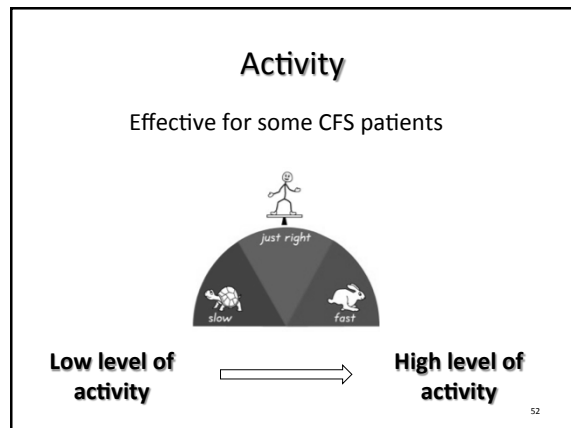
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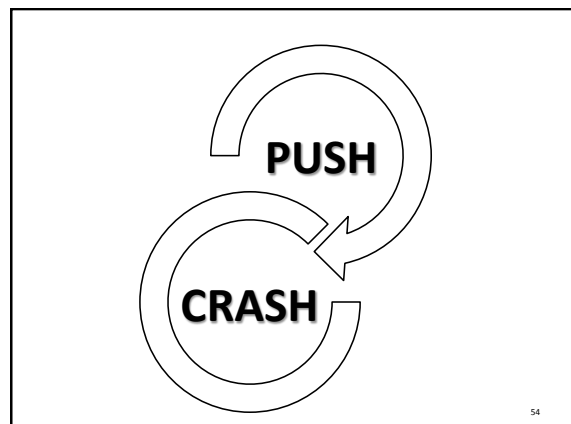


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Activity Pacing



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Activity

- Low level → high level
- Should not feel tired following activity
- If symptoms worsen after activity → return to last level that was comfortable
- Stretching & lifting light weights
 - Precede aerobic activity



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Graded Exercise Therapy

- Active stretching
 - Range-of-motion movements
- Start at 5 min/day

Balance activity and rest

Add time/repetitions – stop before patient gets tired

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Goals of Graded Exercise Therapy

Prevent fatigue

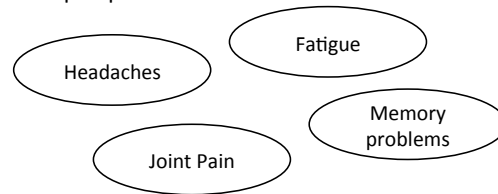
Avoid activating syndrome

Increase overall fitness

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Sleep Concerns

- Problems sleeping common in CFS
 - Treat early
- Sleep deprivation:



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Sleeping Tips

- Schedule regular sleep & wake times
- Establish bedtime routine
- Avoid naps
- Incorporate wind-down period
- No TV, reading, or computers in bed

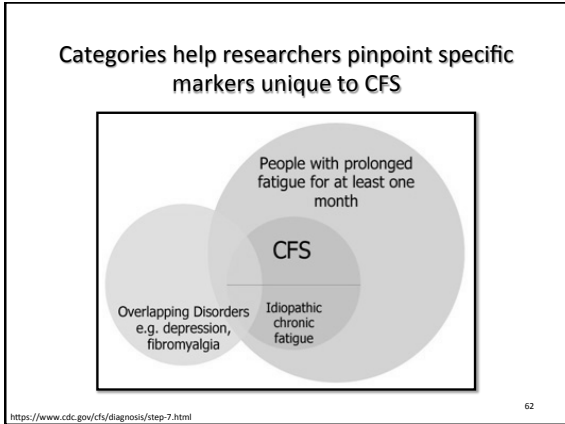
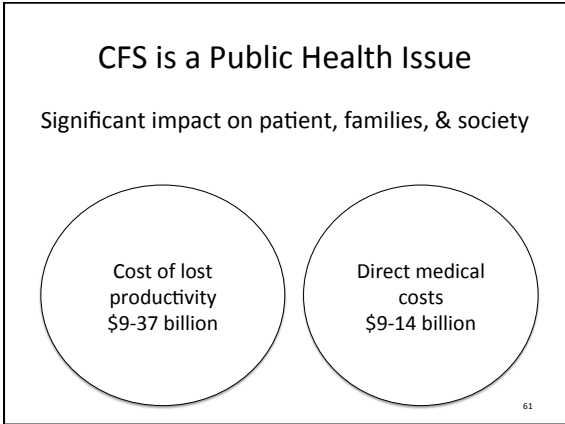


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Sleeping Tips

- Avoid:
 - Caffeine (6 hrs before bedtime)
 - Alcohol & tobacco (2 hrs before bedtime)
- Control light, noise, & temperature
- Light exercise/stretching at least 4 hours before bedtime helps
- If unsuccessful – pharmaceutical drugs may be indicated

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- ### Addressing CFS
- Institute of Medicine (IOM)
 - Panel of physicians issued 300-page report in which they reviewed ~9000 articles
 - Proposed changing name of CFS to “systemic exertion intolerance”
 - Concluded that “CFS is a serious, chronic, complex systematic disease that can often profoundly affect the lives of patients”
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- ### IOM proposed new case definition in 2015
- Patient has 3 symptoms at least half the time (mod-severe degree):
 - Substantial reduction/impairment to engage in activities for >6 mos & accompanied by profound fatigue
 - Postexertional malaise
 - Unrefreshing sleep
 - Plus, at least one of the following manifestations (chronic/severe):
 - Cognitive impairment
 - Orthostatic intolerance
- Institute of Medicine (2015). Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington, D.C.: The National Academies Press. <http://www.nationalacademies.org/hmd/reports/2015/mecfs.aspx>
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- ### Addressing CFS
- National Institute of Health (NIH)
 - Held a Pathways to Prevention workshop
 - Recognized that CFS is not primarily a psychological illness (NIH & IOM)
 - Agency for Healthcare Research & Quality
 - Reviewed published research on diagnosis & treatment of CFS
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NIH Intramural Program

(began in Sept. 2015)

Hypothesis:

“CFS is attributable to an infection that results from immune-mediated brain dysfunction in some patients with acute onset illness”

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NIH Intramural Program

Goal #1: Define the clinical phenomena based on:

- History
- Physical exam
- Neurological assessment
- Neurocognitive testing
- Psychiatric evaluation
- Infectious disease
- Rheumatologic evaluation
- Neuroendocrine evaluation
- Exercise testing

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NIH Intramural Program

Goal #2: Define physiological basis of post exercise fatigue & malaise:

- MRI
- Metabolic studies
- Transcranial magnetic stimulation
- Autonomic testing before and after exercise

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NIH Intramural Program

Goal #3: Determine presence of abnormal immune parameters in blood and CSF & look for any changes in microbiome profiles

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NIH Intramural Program

Goal #4: Determine if features of the illness can be reproduced using the cells or serum from patients

- Variety of approaches using pluripotent stem cell-derived neurons

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CDC

- Provides evidence-based information to health care professionals
- Paired with Medscape to provide roundtable discussions
- Provided free online courses
- Developed content for MedEd Portal (free service for medical school faculty)

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CDC

- Patient-centered outreach & communication calls
 - Teleconference offered twice/year
- Developing educational materials
 - Collaboration with other stakeholders
 - Disseminate into medical community
 - Many clinicians do not fully understand CFS

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NIH Recognition of Further Research for CFS

Previous clinical studies:

- Focused on predominately white, middle-aged women
- Excluded rural communities
- Small & took place in specialty clinics with homogeneous populations

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What is needed:

- To what degree does self-management improve health & Quality of Life
- Standardized, validated tools & measures
- Retrospective, prospective, & longitudinal studies
- Biological factors underlying disease onset

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Conclusion

CFS is significant burden on patients

Should continue to be an area of active research

Health care providers need to be aware of the significance of CFS

Continued outreach, communication, & education

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References

- Chronic Fatigue Syndrome. <https://www.cdc.gov/cfs/index.html>
- Green, C.R., et al., (2015). National Institutes of Health pathways to prevention workshop: Advancing the research on myalgic encephalomyelitis/chronic fatigue syndrome. *Annals of Internal Medicine*, 162(12).
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