



Solve ME/CFS Initiative

Leveraging patient-centered
research to cure ME/CFS

2015 Webinar Series | Thursday, June 18, 2015 | 1:00 PM Eastern

Post-Exertional Malaise: History, Characteristics, Evidence

Lily Chu, MD, MS

Co- Vice President, International Association for
Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Stanford University ME/CFS Initiative Community
Advisory Board Member



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Post-exertional Malaise : History, Characteristics, Evidence

Lily Chu, MD, MS – June 18, 2015

Overview

- ❑ Origins and evolution
- ❑ Definitions of post-exertion malaise (PEM)
- ❑ Evidence: Clinician experience/ patient reports/ research highlights
(IOM Book: download/ read online for free
http://books.nap.edu/openbook.php?record_id=19012)
- ❑ Talking to your doctor / others about PEM
- ❑ Future research

Origin and evolution 1

- ❑ 1955 – London Royal Free Hospital (Ramsey)
- ❑ “Muscle fatigability, whereby, even after a minor degree of physical effort, three, four or five days, or longer, elapse before full muscle power is restored and constitutes the sheet anchor of diagnosis. Without it I would be unwilling to diagnose a patient as suffering from ME, but it is most important to stress the fact that cases of ME of mild or even moderate severity may have normal muscle power in a remission. In such cases, tests for muscle power should be repeated after exercise.”
- ❑ Fluctuating course, cognitive stressors, incautious continuation = chronic symptoms
- ❑ (<http://www.cfids-me.org/ramsay86.html>)

Origin and evolution 2

- ❑ **1988 – Holmes criteria:** “Prolonged (24 hours or greater) generalized fatigue after levels of exercise that would have been easily tolerated in the patient's premorbid state”
- ❑ **1994 – Fukuda criteria:** “post-exertional malaise lasting more than 24 hours” [no definition of malaise; most used]
- ❑ **2001 – King et al.:** “no clear operational definition of this symptom [PEM] exists”
- ❑ **2003 – Canadian Consensus Criteria (CCC):** “inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. slow recovery period - usually 24 hours or longer”

Origin and evolution 3

- ❑ 2011 – Myalgic Encephalomyelitis – International Consensus Criteria (ME-ICC):
 1. Marked, rapid physical and/or cognitive fatigability in response to exertion (minimal such as activities of daily living or simple mental tasks)
 2. Symptom exacerbation: e.g. acute flu-like symptoms, pain, and worsening of other symptoms
 3. Immediately or delayed by hours or days.
 4. 24 hours or longer usually
 5. Low threshold of fatigability = substantial reduction in activity level.

Origin and evolution 4

- ❑ 2012 (?) – CDC website:
- ❑ “increased malaise (extreme exhaustion and sickness) following physical activity or mental exertion”

What is PEM? - 1

	Ramsey	Holmes	Fukuda	CCC	ME-ICC
Name	None	“Generalized fatigue”	“PEM”	“PEM and/or post-exertional fatigue”	“Post-exertional neuroimmune exhaustion”
Required?	Yes	No	No	Yes	Yes
Cognitive exertion?	Yes	No	No; now Yes	Yes	Yes
Trigger intensity?	“Minor degree of physical effort”	Less than previously tolerated activity level	Not specified	“Inappropriate” “After relatively normal”	“minimal activity” “Activities of daily living”

What is PEM? - 2

	Ramsey	Holmes	Fukuda	CCC	ME-ICC
Onset	Not specified	Not specified	Not specified	“delayed..... next day or later”	Immediate or delayed hours to days
Symptoms other than physical fatigue	Muscle fatigability	None	“sickness” (2012)	Cognitive fatigue/ stamina loss, “patient cluster”, “influenza”; “sore throat”, pain	Cognitive fatigability, pain, flu-like symptoms, worsening of “other sx.”
Duration	3 to 5 days	“Prolonged (24 hours or greater)”	More than 24 hours	“usually more than 24 hrs.” but “varies” also	“usually” more than 24 hrs.; up to weeks

IOM: Re-constructing/ updating PEM

- ❑ Clinician experience
- ❑ Patient reports
- ❑ Study examples: Ch. 4, PEM section
 - Some stressor applied
 - Patient-reported symptoms
 - Compared to controls
 - Objective outcomes as possible

Clinical experience

- ❑ Prior case definitions
- ❑ Committee discussions
- ❑ IOM public presentations

Patient Reports 1

*“When I do **any activity that goes beyond what I can do** - I literally **collapse** - my body is in **major pain**, it hurts to lay in bed, it **hurts to think**, I can't **hardly talk** - I can't find the words, I feel my insides are at war. My **autonomic system** is so out of whacked! I can't see farsighted and glasses won't help - only rest. My **GI system** is so messed up. My **body jerks**. the list goes on. There are **days** that I just want to cry because **I can't take care of myself** - I need help.”* (IOM public comment, p.78)

Patient Reports 2

❑ Triggers:

- “something that you can normally undertake” – out-of-proportion reaction
- cognitive/ physical exertion; poor sleep; infections; weather changes; massage; upright position; emotional distress

❑ Timing:

- start “within a few minutes of an activity or even days after”
- difficulty recovering strength/ energy following exertion
- exacerbation lasts days to years (FDA Voice of the Patient)

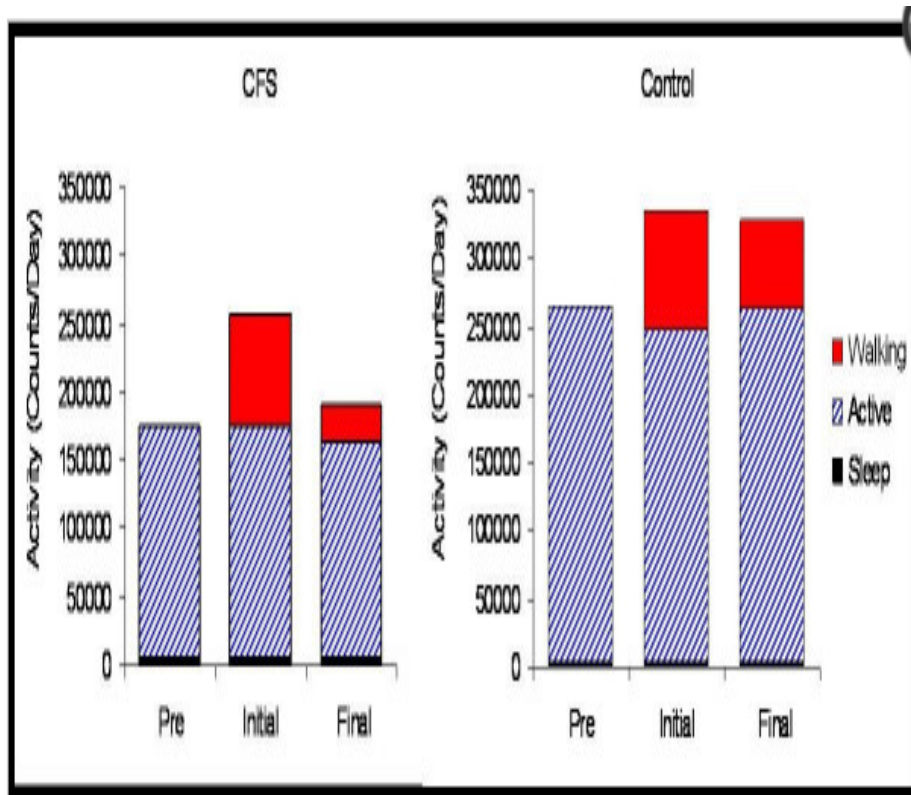
Patient Reports 3

❑ Other Features:

- unpredictable; varies between and within persons
- “lots of smaller triggers can build up over time and cause a bigger crash.”

(FDA Voice of the Patient)

1. Black, 2005: Trigger, onset



- Increase walking 30% from baseline
- Activity monitors
- Both groups increase initially
- ME/ CFS activity decreased days 4-10
- Mild trigger; delayed onset; objective outcome

2. VanNess, 2010: PEM symptoms, duration

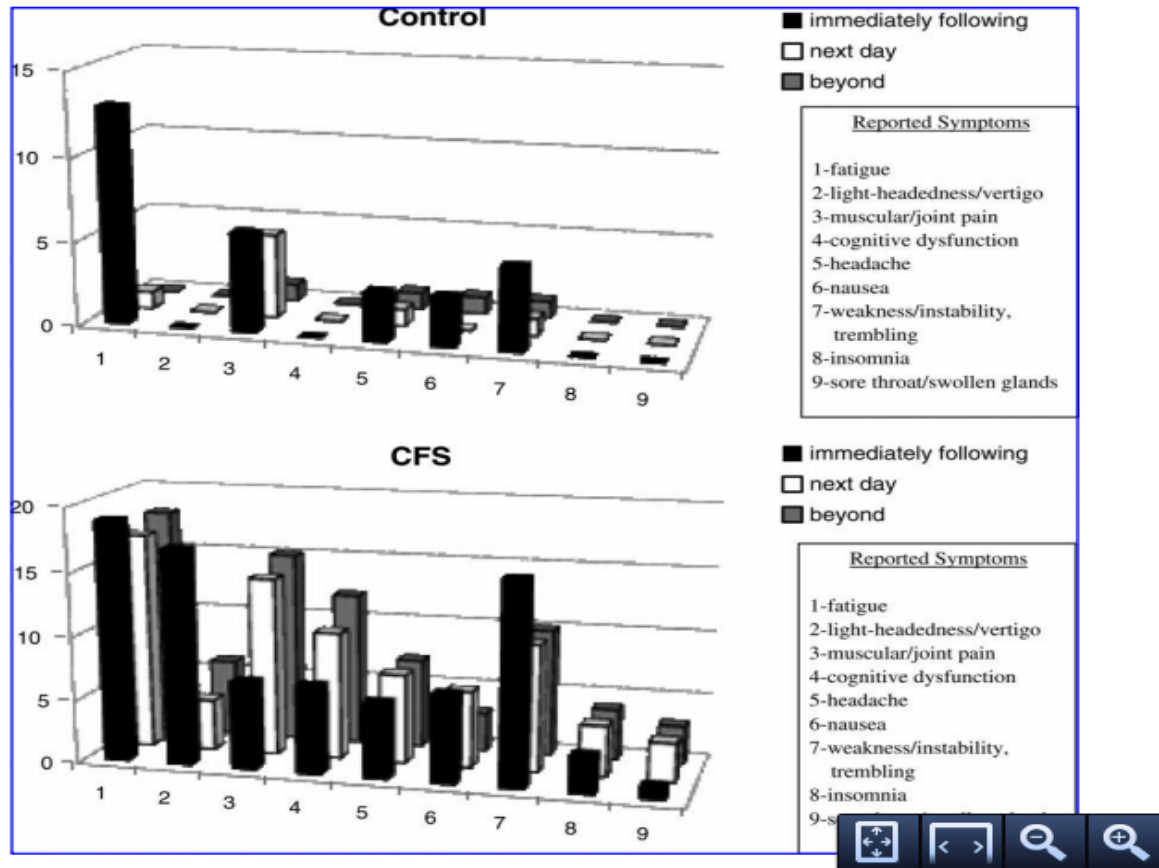


FIG. 1. Reported symptoms following the exercise challenge. Self-reported symptoms immediately after the exercise test, the day after the exercise test (next day), and up to 7 days after the exercise test (beyond). CFS, chronic fatigue syndrome.

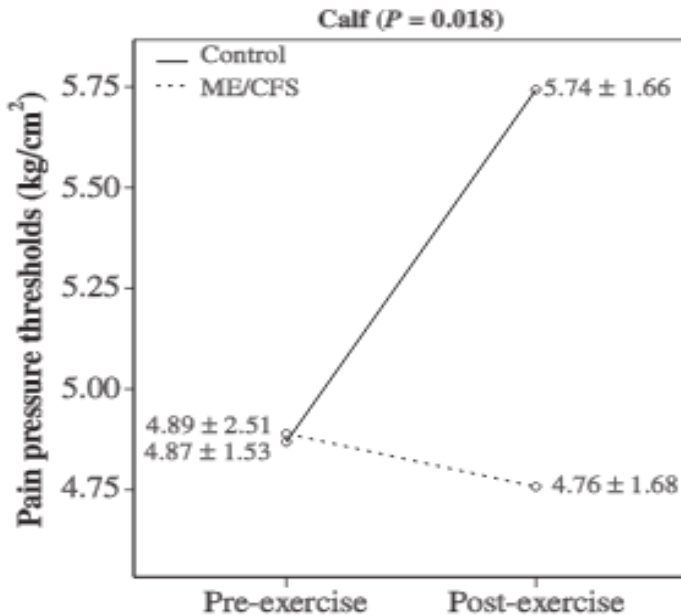
ME/ CFS subjects:

- more diverse/severe symptoms
- 60% took 5 or more days to recover vs. 87% healthy in 24 hrs.
- 0% feel better vs. 75% healthy felt better after biking

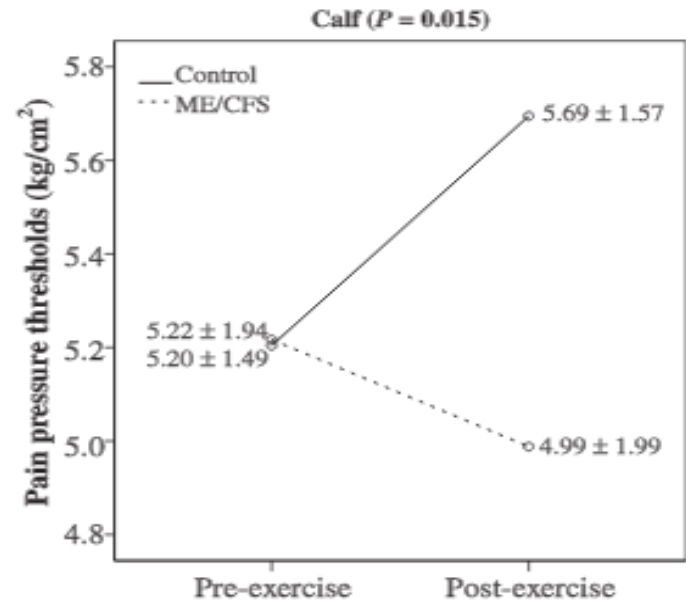
(IOM, p.78, 84)

3. Nijs, 2010: Pain paradox, trigger

Researcher-determined limits



Subject-determined limit



Solid line = healthy sedentary
Dashed line = ME/CFS

(IOM, p.85)

\$245



4. Togo, 2011: Sleep, subgroup



- ❑ Sleep studies; subjects rated sleepiness, fatigue, pain before and after each study
- ❑ **Healthy /ME/CFS – less sleepy: Improved** continuity, deep sleep, efficiency; reduced sleepiness/ fatigue AM after post-bike
- ❑ **ME/CFS-more sleepy : No change** in continuity/ efficiency; sleepiness/ fatigue (IOM p.94)

5. Cockshell, 2014: Cognitive exertion, duration

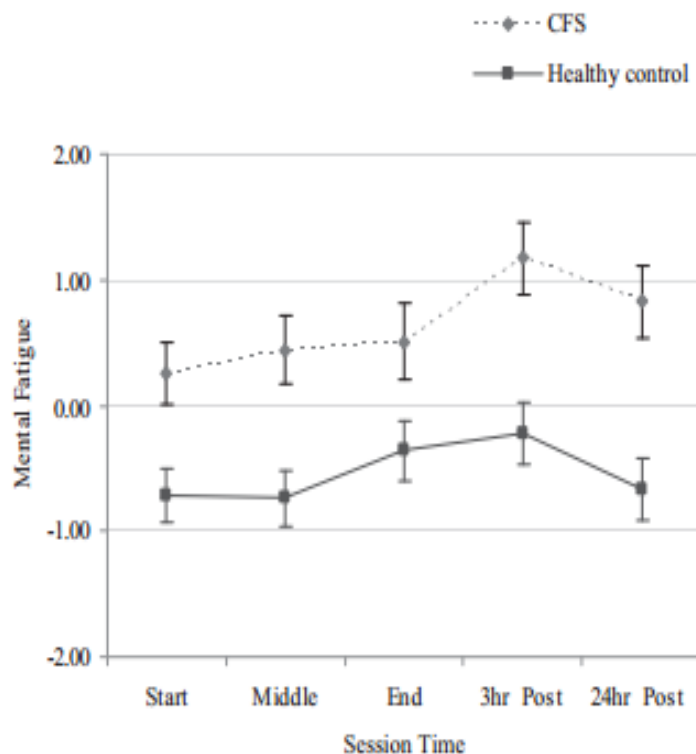
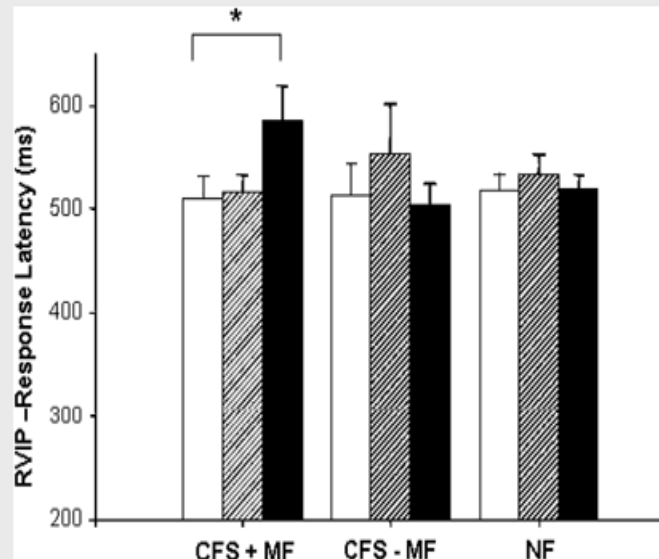


Figure 2. Mean ratings of mental fatigue with 95% confidence intervals, during and after the cognitive testing session for the CFS and healthy control groups.

- ❑ Neuropsychological testing over 3 hours
- ❑ Assessed subject-rated mental fatigue during different times
- ❑ Healthy recovered within 7 hrs. post-test vs. CFS 57 hrs. post-test

(IOM, p.84)

6. Capuron, 2006 : Cognitive exertion, performance



Change in response latency (ms) over the course of the RVIP test in patients with CFS and significant complaints of mental fatigue (CFS+MF), patients with chronic fatigue and low mental fatigue (CFS-MF), and nonfatigued subjects (NF). White bar: first period of the test (trials 1-9, ie, min 2); striped bar: second period of the test (trials 10-18, ie, min 3); solid black bar: third period of the test (trials 19-27, ie, min 4). Only CFS patients with significant complaints of mental fatigue exhibited increased response latencies between the first and last periods of the test (mean increase=78 ms). * $P < 0.05$ period 1 vs period 3.

RVIP = rapid visual information processing; deficits also seen in working memory; look for effects in subjects endorsing presence of/ greater symptoms. (IOM, p. 84)

7. Two Cardiopulmonary Exercise Tests Separated by 24 hrs.: Recovery

(IOM, p.82-33)

Comparing Day 1 to Day 2 CPET	Maximal threshold - Oxygen uptake	Maximal threshold - Workload	Anaerobic threshold - Oxygen uptake	Anaerobic threshold - Workload
VanNess (2007)	--22%	N/A	--26%	N/A
Vermeulen (2010)	--6%	--5%	-- 7%	--8%
Snell (2013)	-- 5%	-- 7%	--11%	-- 55%
Keller (2014)	--14%	--13%	--16%	--21%

- Healthy and many sick people have difference of less than 7%
- Some healthy people IMPROVED measures on the second test
- Poor effort not an issue due to maximal effort confirmed biologically

Effects of physical activity 1

Factor	ME/CFS subjects	Healthy/ sick controls
Fatigue	Worsened cognitive/ physical fatigue	May be worse initially but quick recovery
Pain	Pain outside of exercised areas	Pain in exercised areas
	Decreased pain threshold	Increased pain threshold
Sleep	Improved in some; no change in others	Improved

Effects of physical activity 2

Factor	ME/CFS subjects	Healthy/ sick controls
Cognition	Worsened symptoms/ performance in some	Improved
Mood	Worsened mood/ disturbances	Improved
Other symptoms	Sore throat, tender lymph nodes, “flu-like” feelings, gut,	Not seen / other symptoms noted
Recovery	Prolonged, esp. relative to inciting activity	Relatively quick once activity stops

Is PEM unique to ME/ CFS? (IOM, p.184, 80)

- ❑ 69% - 100% adults ME/ CFS; 71%-97% kids ME/CFS
- ❑ 2%-19% healthy adults
- ❑ 52% (?) multiple sclerosis
- ❑ 19%-64% (?) major depression
- ❑ Distinguishes from idiopathic chronic fatigue
- ❑ Depends on case definition used/ how questions phrased; whole presentation used for diagnosis

IOM PEM Definition:

“PEM is worsening of a patient’s symptoms and function after exposure to physical or cognitive stressors that were normally tolerated before disease onset. Subjective reports of PEM and prolonged recovery are supported by objective evidence in the scientific literature, including failure to normally reproduce exercise test results (2-day cardiopulmonary exercise test) and impaired cognitive function after exertion.” (IOM Clinician Guide)

Communicating with your doctor

- ❑ Goal: understand PEM's impact on your life
- ❑ Time limits – 15-20 minute visits
- ❑ Prepare – keep a short diary/ share notes
- ❑ Describe:
 - Triggers (type, degree)
 - Symptoms (variety, severity)
 - Timing (onset, duration, recovery)
 - Activities avoided/ reduced/ adapted

PEM and banking: an analogy

Dollars = energy

Healthy: \$100 daily

ME/CFS: \$50 daily

Dollars can be spent in any way



- ❑ Overspend & get an overdraft penalty = PEM
- ❑ Save & earn interest = pace/ rest and perhaps a bit more energy SO work on “budgeting” energy
- ❑ The “interest rate” for healthy people may be higher than it is for ME/CFS patients. (i.e. not as much benefit from rest)

Future Directions: PEM Research

- ❑ Stressors: try others; standardize
- ❑ Controls: healthy sedentary; other illnesses
- ❑ Symptoms: ask; not just fatigue; open-ended ?s
- ❑ Timing: onset, course, duration, longitudinal
- ❑ Objective measures: Repeated exercise test, neuroimaging, cognitive tests, activity monitors, immune function, etc.
- ❑ Diverse subjects; men, children, minorities, community-based, etc.

Conclusions

- 1) Lack of/ unclear/ diverse definitions of PEM in the past might have led to neglect/ confusion.
- 2) The IOM Committee defined PEM based on clinician, patient, and researcher input.
- 3) The triggers/ symptoms/ timing and commonality of PEM in CFS are distinctive. People with CFS appear to react differently to exertion compared to healthy and other sick people.
- 4) Consider emphasizing these differences when explaining PEM to others.
- 5) More and higher-quality research is urgently needed.

Thank you for your attention!



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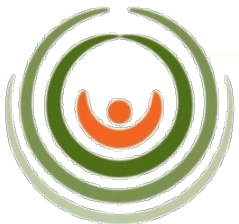
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Solve ME/CFS Initiative

Leveraging patient-centered
research to cure ME/CFS

Thank You!

Our Mission:

Make ME/CFS understood, diagnosable and treatable.

Our Strategy:

Stimulate participatory research aimed at the early detection, objective diagnosis and effective treatment of ME/CFS through expanded public, private and commercial investment