

Diagnosis and Treatment of Fatigue in Inflammatory Bowel Disease

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Disclosures

- Research support (subinvestigator on protocols)
 - Janssen – trials ongoing
 - Abbvie – trial ongoing
 - Arena/Pfizer – trials ongoing
 - Eli Lilly – trial ongoing
 - Takeda – trial completed in 2025
 - Bristol Myers Squibb – trial ongoing
 - PROCISE diagnostics – collaboration completed in 2024
- Consulting
 - Takeda – ad board for cyclic vomiting 2020
 - Eli Lilly – consulting since 2019
 - Fresenius Kabi – drug development - 2022
 - Alivio therapeutics- drug development – 2023
 - Blue Cross Blue Shield formulary committee - 2023
- Honoraria and Royalties
 - Up to Date – Royalties
 - Boston University – honorarium

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Definition of Fatigue

- “Overwhelming and sustained sense of exhaustion that decreases one’s capacity for physical and mental work.”
- Multidimensional components of fatigue
 - Generalized weakness (or perception of generalized weakness)
 - Motivational component
 - Inability to initiate activities
 - Reduced capacity to maintain activities once initiated
 - Mental component – impaired concentration and memory
- Impact on Activities of Daily Living
 - Missed School and Work
 - Diminished self-care

Crichton et al, Pediatrics 2015; 135:e105
Borren et al, Nature Reviews Gastro Hep 2019; 10: 247

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Fatigue – patient voices

The fatigue is absolutely killing me off. It's not only tiredness, it's muscle pain, brain fog, joint pain, all of it. I feel like I'm wasting my life and I can't be the parent or the partner I wish I could be.

I get so tired it's exhausting to lay in bed!

I've had many, many days where the fatigue was so bad I couldn't shower, because I didn't think I could stand for more than two minutes. Keeping my apartment clean is a nightmare. Going grocery shopping is something I have to spend days preparing for, and it takes me days to recover from.

To understand the fatigue of someone living with Crohn's or Colitis, a healthy person would need to stay awake for three days straight and then try to function like normal.

Crohn's fatigue isn't "just tired."
It's waking up exhausted.
Running out of energy quickly.
Feeling drained after simple tasks.
And the frustrating part?
Most people can't see it.

It feels like your phone is always in the red zone and not charging.

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Epidemiology of Fatigue

- Adults – General Population
 - 8% of adults have fatigue - common complaint in primary care
 - Up to 7 million physician visits per year in the USA
 - Costs of lost work over 100 billion dollars per year
- Adults with IBD
 - Up to 80% of adults with IBD have had fatigue complaints
 - Up to 50% of adults with IBD in remission have fatigue
 - Up to 20% have chronic fatigue (persistent fatigue greater than 6 months)
- Children – general population
 - 5-10% have "general fatigue"
 - 1-2% have chronic fatigue greater than 6 months.
- Children with IBD
 - 80% report of children or their parents report fatigue
 - 30% report "severe fatigue"

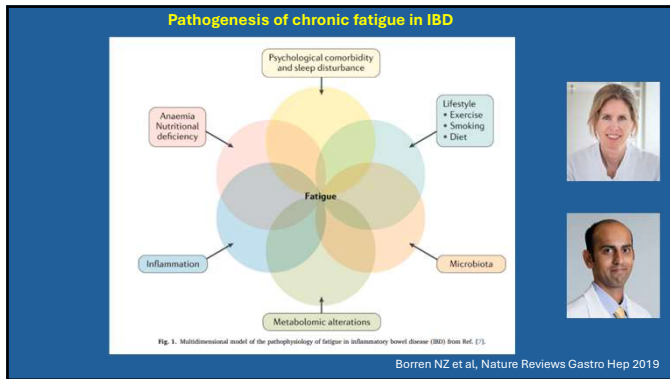
Yoon et al, Front Pub Health 2023
Borren NZ, Nature Gastro Hep 2019

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Risk Factors for Fatigue

- Chronic illness
 - Cancer – best studied
 - Neurologic - Multiple Sclerosis
 - Inflammatory - Rheumatoid Arthritis, IBD
 - Cardiac disease – Heart failure
 - Chronic obstructive pulmonary disease
 - Infectious and post-infectious (e.g. Long COVID)
 - Obesity
- Chronic fatigue syndrome / "myalgic encephalomyelitis"
- Psychiatric (anxiety/depression)
 - But many patients with fatigue do NOT have anxiety or depression
- Female gender
- Autonomic dysfunction (postural orthostasis tachycardia syndrome)
- Sleep disturbance

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Studies of pathophysiology have failed to find a single or definitive mechanism of fatigue

- Inflammation**
 - While active inflammation or cancer correlate with fatigue, patients in remission also have chronic fatigue.
 - Different cytokines (IL-6, TNF have been studied) without differences
- Microbiome**
 - Probiotics can improve microbial diversity without improving fatigue.
- Hypothalamic pituitary axis**
 - No major differences in serum cortisol
- Micronutrients**
 - Some fatigue patients DO have micronutrient deficiencies
 - However, studies have failed to find convincing differences in iron, B12, thiamine or other micronutrients in patients with or without fatigue.
- Anxiety and depression**
 - Prevalence is 25% in patients with IBD (less than the prevalence of fatigue).

Matura et al Biological Research for Nursing 2018;20:410

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Measuring fatigue – FACIT scale

Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1 I feel fatigued	0	1	2	3	4
2 I feel weak all over	0	1	2	3	4
3 I feel listless ("washed out")	0	1	2	3	4
4 I feel tired	0	1	2	3	4
5 I have trouble starting things because I am tired	0	1	2	3	4
6 I have trouble finishing things because I am tired	0	1	2	3	4
7 I have energy	0	1	2	3	4
8 I am able to do my usual activities	0	1	2	3	4
9 I need to sleep during the day	0	1	2	3	4
10 I am too tired to eat	0	1	2	3	4
11 I need help doing my usual activities	0	1	2	3	4
12 I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13 I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much. EXCEPT items #7 and #8 which are reversed scored. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Visual analogue scale
 Choosing Life, Health and Quality of Life Outcomes
 2015; 13:91

"If you don't take a temperature, you can't find a fever"
 Samuel Shem MD
 The House of God

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Measuring Fatigue

Multidimensional Fatigue Inventory Scale

Instructions: Circle the number next to each item that best describes you currently.

Item	Not at all	A little	Moderately	Quite a bit	Extremely
1. I have trouble remembering things	0	1	2	3	4
2. My muscles ache	0	1	2	3	4
3. I feel upset	0	1	2	3	4
4. My legs feel weak	0	1	2	3	4
5. I feel cheerful	0	1	2	3	4
6. My head feels heavy	0	1	2	3	4
7. I feel lonely	0	1	2	3	4
8. I feel nervous	0	1	2	3	4
9. I feel relaxed	0	1	2	3	4
10. I feel proud	0	1	2	3	4
11. I am confused	0	1	2	3	4
12. I am worried	0	1	2	3	4
13. I feel sad	0	1	2	3	4
14. I feel happy	0	1	2	3	4
15. I have trouble paying attention	0	1	2	3	4
16. My arms feel weak	0	1	2	3	4
17. I feel sluggish	0	1	2	3	4
18. I feel alone	0	1	2	3	4
19. I ache all over	0	1	2	3	4
20. I am unable to concentrate	0	1	2	3	4
21. I feel depressed	0	1	2	3	4
22. I feel refreshed	0	1	2	3	4
23. I feel tense	0	1	2	3	4
24. I feel energetic	0	1	2	3	4
25. I make more mistakes than usual	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4
27. I am forgetful	0	1	2	3	4
28. I feel tired	0	1	2	3	4
29. I feel calm	0	1	2	3	4
30. I am stressed	0	1	2	3	4

Multidimensional Fatigue Symptom Inventory-short form. The fatigue symptom inventory/multidimensional fatigue symptom inventory © 1998 by H. Lee Moffitt Cancer Center and Research Institute, Inc. is licensed under CC BY-NC-ND 4.0. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

Donovan, K. A. et al Support Care Cancer 2015; 23: 191-212

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Treating Fatigue - Overview

- Treat inflammation – induce and maintain clinical remission
 - Biologics, surgery if needed
- Treat anemia and iron deficiency
 - Oral and IV iron
- Evaluate for other micronutrient deficiencies
 - Vitamin D, Vitamin B12
- Think outside the IBD
 - Celiac disease
 - Endocrinologic causes (hypothyroidism, adrenal insufficiency)
 - Cardiovascular causes (postural orthostasis)
 - Disordered sleep – obstructive sleep apnea
 - Psychiatric comorbidities (anxiety, depression)
- Use complementary therapies
 - Cognitive Behavioral Therapy, Electroacupuncture, Probiotics
 - Graduated increase in physical exercise
- Evidence supporting all of these to treat chronic fatigue is poor or limited

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First, assess and treat inflammation

- History and examination
 - Orthostatic blood pressure
 - Thyroid palpation
- Standard labs (CBC, ESR, CRP)
- Fecal Calprotectin
- EGD/colon
- MRI or Capsule (If needed)
- Fatigue is present in
 - 72% of IBD patients with active inflammation
 - Correlation is better in Ulcerative Colitis (Mayo Score)
 - Still present in 47% of patients in remission

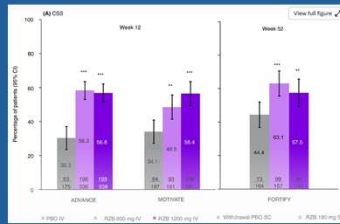
D'Silva et al, Clin Gastro Hep
2022;20: 995-1009



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Does biologic treatment of active IBD improve fatigue?

- Yes, but not a “home run”
- Not every study uses FACIT-F to assess fatigue
- QOL scales such as IBDQ/SF-36 may not be sensitive enough to assess fatigue.
- In clinical trials, about 1/3 of patients who achieve remission still have fatigue.



Percent of patients reporting fatigue improvement On FACIT-F in the Risankizumab Crohn clinical trials

Peyrin-Biroulet et al, APT 2023: 57:496

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Does treating iron deficiency in IBD improve fatigue?

- We believe so, but we don't know.
- Treating anemia helps fatigue in other diseases.
- Meta-analysis of iron deficiency treatment in IBD (Sartain)
 - Only 12 studies of iron deficiency treatment used fatigue specific scales in (FACIT-F, MFI, Piper) in their protocols
 - Approximately 50% found correlation between anemia and fatigue
 - Only 2/12 studies found a correlation between fatigue and iron deficiency without anemia.
- AGA and ECCO recommend IV iron for anyone with a hemoglobin under 10mg/dL or active disease.

Sartain S et al, PLOS-One 2025:E 20(1): e0304293

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Correlation of other micronutrient deficiencies and fatigue is even weaker

- Consider comprehensive assessment of micronutrients
 - Vitamin D (25-hydroxy), vitamin B12, zinc
- Most studies of nutrient supplementation have been done in cancer or MS
- Nutrient therapies in fatigue studies have included:
 - Vitamin C – 500 mg daily
 - Vitamin D – 50000 units weekly
 - CoQ10 – 60-200 mg daily
 - L-carnitine – 50 mg- 2 gram daily
 - NADH
 - Thiamine (IBD trial) 600-1800 mg per day

Barnish et al, Nutrients 2023;15:2154

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Probiotic clinical trial in IBD and fatigue

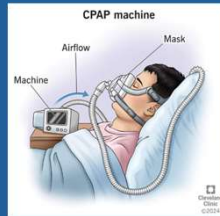
- Randomized clinical trial
- 100 patients with IBD (52 CD) in clinical remission, but with chronic fatigue.
- Supplemented with probiotic containing 40 billion bacteria (Bifidobacteria and Lactobacilli) vs. Placebo for 12 weeks
- 29% of the probiotic group reported improvement in fatigue vs. 40% of the placebo group.



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Sleep apnea in IBD

- In one prospective study of adults, 14% had a history of obstructive sleep apnea (OSA).
- Symptoms
 - Persistent fatigue, fatigue upon waking
 - Falling asleep
 - Snoring
 - Audible gasping at night.
- Risk factors for OSA
 - Older Age
 - Obesity
 - Male Sex
 - If female, postmenopausal
 - Abnormal craniofacial anatomy
 - Macroglossia and micrognathia
- Treatment with CPAP for over 6 hours per night reduces symptoms of fatigue in patients with OSA.
 - No benefit if CPAP used for less than 4 hours per night.



Valentin et al, IBD Journal 2023; 29:207

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Postural orthostasis and tachycardia syndrome (POTS)

- Fatigue is one of the most common comorbid symptoms associated with POTS.
- Diagnosis of POTS involves:
 - **Excessive orthostatic tachycardia** — HR rise ≥ 30 bpm from supine baseline (≥ 40 bpm for ages 12–19) within 10 minutes of standing or head-up tilt.
 - **No orthostatic hypotension** — BP must be maintained; a sustained systolic drop ≥ 20 mm Hg indicates orthostatic hypotension, not POTS.
 - **Chronic orthostatic-intolerance symptoms** — lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue that occur with standing and improve when supine, present for ≥ 6 months
- Treatment
 - Exercise training
 - Salt supplementation
 - Medications (e.g. midodrine)

Sheldon et al Heart Rhythm. 2015 May 14;12(6):e41–e63
via Open Evidence

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Therapy of chronic fatigue syndrome

- Institute of medicine criteria for chronic fatigue syndrome
 - Substantial reduction/impairment in the ability to engage in pre-illness levels of activity
 - Present for at least 6 months
 - Worsening of symptoms after physical, cognitive or emotional exertion
 - Unrefreshing sleep
 - Plus cognitive impairment or orthostatic intolerance.
- CFS is usually not diagnosed in the context of another chronic illness.
- Pharmacologic therapy can be tried
 - Antidepressants, stimulants, CoQ10, carnitine, low dose naltrexone, minocycline
 - No proven or FDA approved pharmacologic therapy for CFS

Fan et al; J. Translational Medicine 2026;34:62

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Cognitive Behavioral Therapy for CFS

- Most commonly utilized intervention to treat chronic fatigue syndrome
- PACE trial of CBT for CFS
 - 24 weeks, with 36 week Booster session
 - Interventions
 - Establish a baseline
 - Set goals
 - Reduce catastrophizing
 - Improve sleep
 - Graded exercise tolerance
- Meta-analysis of 1298 patients
 - Reduced fatigue severity, improved physical functioning
 - Children and young adults benefit most
 - Patients with chronic pain, less physical activity and depression benefited the least.

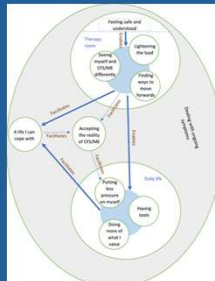


Figure from Health Expectations 2022
White et al, Lancet 2011; 377:823-36
Kunt et al Psychological Medicine 2023

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Conclusions

- Fatigue is a common problem in IBD patients
 - More common in active disease, but still present if patients are in remission.
- Ask about fatigue, or use a scale (FACIT-F) to screen
- Treatment
 - Control disease activity – biologics best, treat to target
 - Consider other causes (thyroid, sleep apnea, postural orthostasis)
 - Assess for micronutrient deficiencies
 - Evaluate and treat for anxiety and depression
 - No proven nutritional, probiotic, or pharmacologic therapy
 - Cognitive behavioral therapy, graduated exercise programs, and acupuncture may be helpful

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