

ABOUT THE AUTHORS



Yaa Danso, MBBS, MRCP, IBD Research Fellow

Dr. Yaa Danso serves as a gastroenterology Registrar and IBD Clinical Research Fellow. Her research explores the impact and associations of fatigue in IBD patients, with a particular focus on investigating novel psychological and psychotropic treatment strategies. Beyond her research, Dr. Danso shares a strong commitment to addressing healthcare disparities and improving outcomes for underrepresented populations within gastroenterology.

Affiliations:

St Mark's Hospital, London, UK
Department of Metabolism, Digestion and Reproduction, Faculty of Medicine,
Imperial College London, London, UK



Prof. Ailsa L. Hart

Professor Ailsa Hart is Director of Inflammatory Bowel Disease (IBD) Research at St Mark's Hospital, Consultant Gastroenterologist, and Clinical Senior Lecturer at Imperial College London. Internationally recognised for her expertise in IBD, Crohn's disease, and ulcerative colitis, she leads one of the UK's largest IBD services, caring for approximately 14,000 patients. A distinguished clinician, researcher, and educator, she has published over 400 peer-reviewed papers and two books. Professor Hart has held senior leadership roles within leading national and international gastroenterology organisations and has delivered invited lectures worldwide. She was recently recognised by *Tatler* as one of the UK's top gastroenterologists.

Affiliations:

St Mark's Hospital, London, UK
Department of Metabolism, Digestion and Reproduction, Faculty of Medicine,
Imperial College London, London, UK



James Alexander, MD

Dr. James Alexander is a Consultant Gastroenterologist at St Mark's Hospital and Honorary Clinical Senior Lecturer at Imperial College London. His clinical and research interests focus on inflammatory bowel disease (IBD), particularly the role of the gut microbiome in disease outcomes and treatment response. He was awarded the British Society of Gastroenterology Young Gastroenterologist of the Year in Clinical and Translational Science in 2023.

Affiliations:

St Mark's Hospital, London, UK
Department of Metabolism, Digestion and Reproduction, Faculty of Medicine,
Imperial College London, London, UK
Department of Gastroenterology, Imperial College Healthcare Trust, London, UK



Calum D. Moulton, MD

Dr. Calum Moulton is a Consultant Liaison Psychiatrist specialising in gastro-psychiatry and complex gut disorders. He trained at Cambridge University, South London and Maudsley NHS Foundation Trust, and completed a PhD in Psychological Medicine at King's College London. He holds an NIHR Advanced Fellowship and leads research focused on fatigue, depression, and gut-brain disorders in inflammatory bowel disease (IBD).

Affiliations:

St Mark's Hospital, London, UK

Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, UK

Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Fatigue in Inflammatory Bowel Disease (IBD): **Diagnostic Workup and Management**

Yaa Danso, MBBS, MRCP, IBD Research Fellow

Prof. Ailsa L. Hart

James Alexander, MD

Calum D. Moulton, MD

Introduction

Fatigue affects up to 72% of patients with inflammatory bowel disease (IBD), including up to 1 in 2 patients whose disease is in remission.¹

Beyond IBD treatments, few therapies for fatigue have been studied. The lack of clear success in clinical trials investigating fatigue treatments in IBD has left many clinicians without the therapeutic arsenal to manage this symptom.

This paper aims to provide a practical roadmap for busy clinicians to understand and incorporate IBD-related fatigue discussions within their consultations.

Recognizing and Assessing Fatigue

The burden of disease for patients often exceeds digestive manifestations, such as diarrhea, rectal bleeding, and pain.² Beyond these, fatigue is one of the most frequently non-gastrointestinal patient-reported complaints, yet remains under-recognized and under-discussed by clinicians.^{2,3} Understanding how to recognize and measure fatigue is an important first step in its management.

Fatigue is more than generic tiredness that can affect both physical and mental functioning. Some level of fatigue is common, but it should not be exhaustive or limiting. The aim of assessment is to recognize that some level of fatigue is expected

Feature	IBD Fatigue Scale (IBD-F)	FACIT-Fatigue
Structure	2 sections: 5 items on frequency/severity of fatigue 30 items on experience/impact of fatigue	13 items total
Item content	Section I: measures both how often fatigue occurs and its severity Section II: measures the impact of fatigue across physical, cognitive, emotional, and functional daily activities	Physical tiredness/weakness items, plus functional-impact items (e.g. energy levels, ability to perform usual activities, need to rest or sleep)
Recall period	2 weeks	1 week
Response scale	0–4 Likert scale	0–4 Likert scale
Direction of score	Higher score = greater fatigue	Higher score = less fatigue
How the total is calculated	Sections scored separately; not combined into one total score Section II has six items with an N/A option; the total is prorated when N/A responses are selected	Sum individual item scores, multiply by 13, divide by the number of items answered Note: Negatively worded items are recoded, so 0 = bad, 4 = good
Score range	Section I: 0–20 Section II: 0–120	0–52 total
Clinically useful cut off	Varies between studies	None (>40), mild (>30 to ≤40), moderate (>21 to ≤30), and severe (≤21) ⁶

Figure 1. IBD-F vs FACIT-Fatigue assessment tools; courtesy of Yaa Danso, MBBS, MRCP, IBD Research Fellow, Prof. Ailsa L. Hart, James Alexander, MD, and Calum D. Moulton, MD.

but fatigue should not be severe enough to impair daily functioning.

A fatigue assessment tool can establish symptom severity and guide further conversations. Two commonly used tools are highlighted above (**Figure 1**). One of these, the IBD Fatigue (IBD-F)⁴ scale, is split into the two sections; the first section incorporates five brief questions that establish fatigue severity over the last 2 weeks. This scale is validated within IBD and can be easily completed by patients before their consultation. Scores range between 0 and 20, with scores of 11 or more suggesting severe fatigue. This tool can be used regularly to track changes in fatigue severity over time. However, within the IBD-F, there is no formal cut off to delineate improvement in fatigue over time.⁴ Subsequent studies have examined this issue and have proposed differing Score1 cut-offs, while others have not identified any threshold.¹ The Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-F)⁵ is an alternative assessment tool. This 13-item questionnaire evaluates fatigue symptoms experienced over the previous week. Because this tool is used across a range of conditions, FACIT-F

scores can be compared with other chronic diseases. However, its more complex scoring may limit its practicality within time pressured clinics.

A practical tip is to build fatigue assessment into routine care for all patients. Doing so ensures that patients understand that fatigue is recognized as an important symptom in its own right and will also help to build our knowledge base of how patients experience fatigue.

Understanding the Mechanisms

Fatigue is well recognized among patients with active disease; however, far more complex is the persistence of fatigue in quiescent IBD.

Fatigue is observed in chronic inflammatory diseases, such as multiple sclerosis and systemic lupus erythematosus, which supports the hypothesis that inflammatory cytokines could contribute to fatigue.⁷ Elevated levels of proinflammatory cytokines have been shown in fatigued patients, further supporting an inflammatory cytokine-mediated mechanism.^{8,9} The brain-gut axis is the bidirectional pathway between the central and enteric nervous systems.

In response to environmental or clinical stressors, proinflammatory cytokines can activate the hypothalamic-pituitary-adrenal axis, leading to cortisol dysregulation in which cortisol is released. These neuroendocrine changes may have systemic effects and can affect the brain, resulting in fatigue.¹⁰ Within healthy individuals, sleep deprivation, which itself exacerbates fatigue, is associated with an increase in circulating proinflammatory cytokines.¹¹

Mood disorders, which can also cause fatigue,¹² are mediated through central neurotransmitters, primarily serotonin (5-hydroxytryptamine), dopamine, and noradrenaline. The synthesis of these neurotransmitters requires the availability of tryptophan and tyrosine.¹³ As branched-chain amino acids (BCAAs) compete with tryptophan and tyrosine for the same transporters to pass the blood-brain barrier, alterations in circulating BCAA levels are hypothesized to influence the availability of these neurotransmitters in the brain, leading to fatigue. Experimental mouse models of colitis have shown new-onset depressive and anxiety-like symptoms after the induction of gut inflammation.^{13,14}

The Diagnostic Workup

The mechanisms underlying fatigue within IBD are not fully understood; however, identifying and addressing potentially reversible causes is a key component of management. A common challenge faced by clinicians is how to proceed when a patient reports fatigue.¹⁵ The following section outlines a practical approach to assessment and management.

Minimizing mucosal disease activity is an important component of fatigue management. Assessing disease activity with endoscopy or imaging can be helpful. However, we suggest doing this only when supported by gastrointestinal symptoms or biochemical markers as fatigue often remains severe in the context of quiescent disease.

In addition to evaluating disease activity, nutritional and hematological investigations can prove useful. Iron deficiency, reflected by low ferritin levels, irrespective of anemia, can be a driver of fatigue. Assessment of vitamin B12 and folate status are relevant for patients with ileal Crohn's disease or post ileal resection.

Extraintestinal manifestations of IBD, primary sclerosing cholangitis, and coexisting

autoimmune disorders such as hypothyroidism are common within the IBD population and should be addressed. A review of medications is also important. Corticosteroids disrupt sleep patterns, and over time may contribute to myopathy and fatigue, while thiopurines are also recognized to cause fatigue in some patients. Although an exhaustive medication review is not necessary in every case, clinicians should be aware of commonly used medications that can impact fatigue.

Psychological comorbidities can coexist with IBD-related fatigue or contribute to fatigue independently. Conditions such as depression and anxiety are potential causes of fatigue and are treatable. Screening tools such as the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) can help identify symptoms of depression and anxiety, respectively. When these conditions are identified, appropriate management should be initiated, either within the multidisciplinary IBD team or by involving primary care.

Non-pharmacological Management

Non-pharmacological therapies require adherence. It is important to recognize that even with an active and willing patient non-pharmacological therapies are not always successful.

Patient-led sleep hygiene techniques can be used successfully prior to and alongside pharmacological therapies. Four key techniques include: **1)** avoiding alcohol and caffeine 4 hours before bedtime; **2)** avoiding 'screen time' in bed and at least one hour prior; **3)** obtaining daytime sunlight exposure to help maintain circadian rhythms; and **4)** maintain a consistent sleeping time and waking time, even if sleep has been poor.^{16,17} Better sleep quality may be achieved through daytime behavioural activation. Measures such as exposure to sunlight and limiting daytime napping help to distinguish between daytime activities and nighttime rest can help regulate circadian rhythms.

IBD-related fatigue can vary in severity over time for the same patient. On days when fatigue is less pronounced, patients may take advantage of this extra capacity to catch up on lost productivity and consequently overexert themselves. While understandable, this all-or-nothing approach is often followed by worsening in fatigue over the following days, precipitating a 'boom-and-bust'

pattern of fatigue.¹ Opting for sustainable regular activity is often more beneficial, although this requires confirmation within a randomized controlled trial (RCT).^{18,19}

Pharmacological Therapies

If sleep is a concern and non-pharmacological therapies have been unsuccessful, the use of nocturnal sedative medications can be considered.

However, we discourage the use of benzodiazepines and Z-drugs (e.g., zolpidem, eszopiclone, and zopiclone), owing to their risk of dependence and their potential to impair state-dependent learning. The latter refers to the phenomenon whereby information learned in a particular internal state is most easily recalled when that same state is reproduced. Consequently, psychological work that is completed while treated with Z-drugs, may not be as readily retained or transferred to periods when the medication is no longer being used.¹

Non-addictive Sedating Medications

Amitriptyline may be particularly useful for patients with comorbid pain symptoms.²⁰ Treatment is initiated at 10 mg taken once nightly (ON), and can be increased to 30 mg as needed.²¹

Mirtazapine, a sedative antidepressant, may be helpful for patients in whom depression or anxiety is prominent, or for those with persistent upper gastrointestinal symptoms such as postprandial fullness or nausea.²² Patients should be advised that daytime sedation can be pronounced during the first week of treatment but often diminishes with continued use.²³ The usual starting dose of mirtazapine is 15 mg ON.²⁴ Notably, the 15 mg dose is generally as sedating as higher doses.²²

Daridorexant, a dual orexin receptor antagonist for the treatment of insomnia, was shown to be generally safe and well tolerated in a 52-week study (not specifically in IBD) and was associated with minimal morning drowsiness.²⁵ The usual starting dose is 50 mg taken ON, though lower doses of 25 mg may be more appropriate for those with liver impairment.

Emerging evidence suggests that melatonin may function as a mediator between gut microbiota disorders and sleep deprivation.²⁶ In the UK, melatonin is licensed for adults over 55 years of age, with a usual starting dose of 2 mg ON, and a maximum dose of 10 mg ON.²⁷

Patients should be advised that sedative medications may cause residual drowsiness the next day, especially during the early stages of treatment. Caution should be explicitly provided regarding activities that require alertness, including driving, operating heavy machinery, or performing skilled tasks. Use of alcohol should be minimized to prevent oversedation.

Alerting medications can also be considered for patients with refractory fatigue, although their use in this context is off-licence. Modafinil is a wakefulness-promoting medication that acts as an atypical dopamine reuptake inhibitor by binding to the dopamine transporter, which increases extracellular dopamine levels in the brain, although its exact mechanism of action is not clearly defined. In the UK, modafinil is licensed for treating narcolepsy, though its use beyond this indication is supported by the Maudsley Guidelines.²³

Modafinil is initiated at 100 mg in the morning, although a lower starting dose of 50 mg may be appropriate for patients who may be more susceptible to side effects (**Figure 2**). The clinical benefits of modafinil are usually rapid, frequently within 1 week. The efficacy of modafinil should be assessed ideally within 8 weeks and should only be continued if it is beneficial and well tolerated.

Modafinil should be avoided in patients with known arrhythmias, cor pulmonale, left ventricular hypertrophy, and moderate-to-severe uncontrolled hypertension.²⁸ Modafinil is contraindicated during pregnancy, owing to associations with birth defects, and it may reduce the effectiveness of some hormonal contraceptives.²⁹ Women of childbearing age starting modafinil should be advised to use appropriate contraception, such as intrauterine devices, barrier methods, depot progestogen preparations, during treatment and for 2 months after discontinuation.

Although the therapies described above have shown potential for managing IBD-related fatigue, evidence from RCTs is currently lacking (**Figure 2**).

Reassessment and Follow-up

If a pharmacological treatment is effective, we recommend ongoing review at 6 month intervals. At present, there is insufficient evidence to guide the duration of pharmacotherapy for IBD-related fatigue, whether using sedative or wakefulness-promoting medications. We follow extrapolated guidance from depression management with antidepressants, which is to continue any effective medication for 6–9 months,

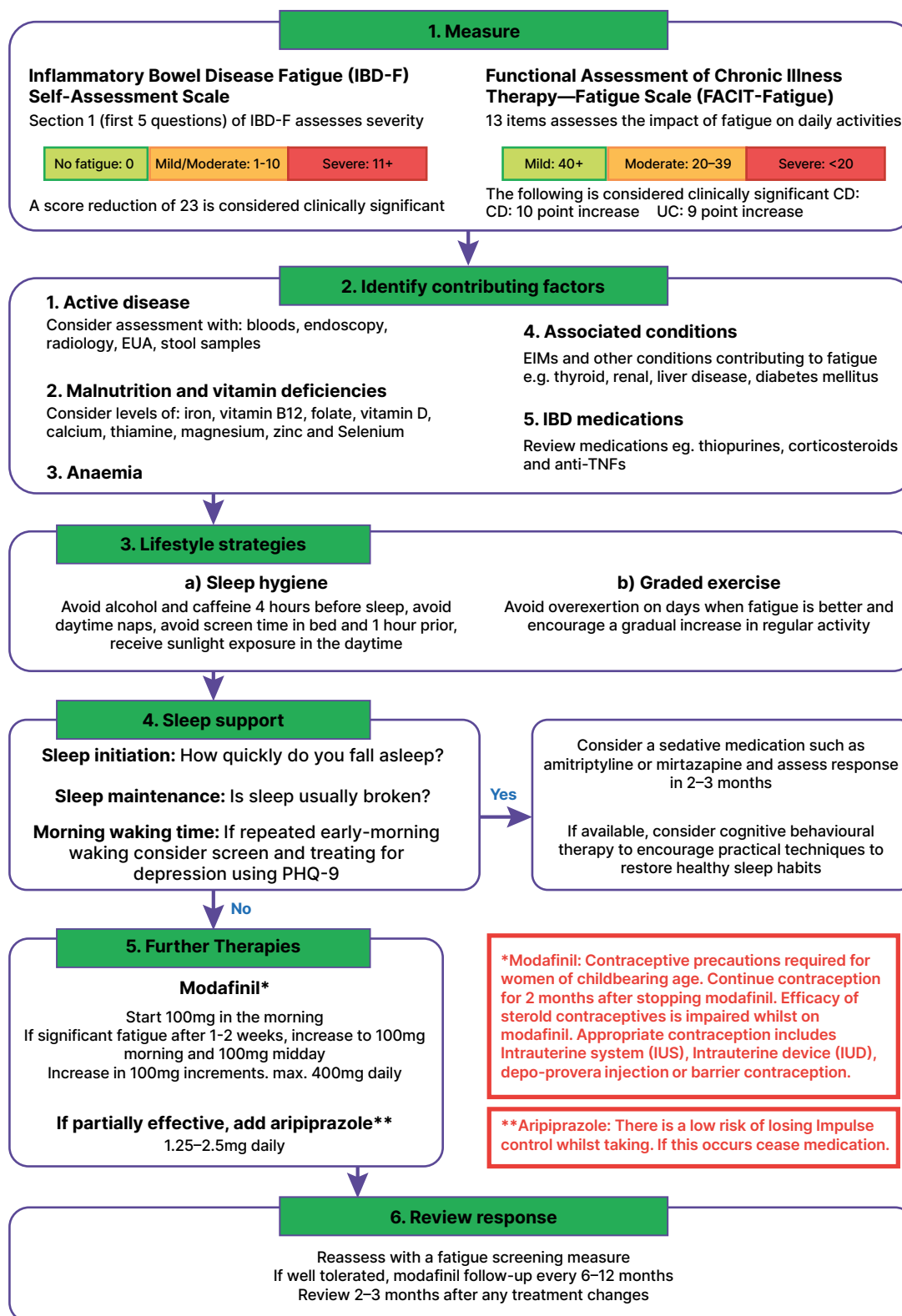


Figure 2. Treatment algorithm for IBD fatigue; courtesy of Yaa Danso, MBBS, MRCP, IBD Research Fellow, Prof. Ailsa L. Hart, James Alexander, MD, and Calum D. Moulton, MD.

Abbreviations: CD: Crohn's disease; EIMs: extraintestinal manifestations; EUA: examination under anaesthesia; PHQ-9: Patient Health Questionnaire-9; UC: ulcerative colitis

before considering dose reduction and/or discontinuation.²⁶ During the initial treatment phase, we suggest reassessing the response at 8 weeks, using the same fatigue assessment tool employed at baseline.

Successful assessment of IBD-related fatigue is not a singular event; rather, it is an ongoing process that requires regular review and dialogue with the patient. Effective management includes a combination of strategies, such as patient-led immediate measures, pharmacological therapies, and the identification and exclusion of other potential contributors to fatigue. Similarly, successful treatment is not a single intervention; we therefore suggest acknowledging and describing this premise at the beginning of treatment, and throughout the treatment course.

Unmet Needs

Despite its high prevalence and significant impact on quality of life, fatigue often remains under-recognized and under-discussed during consultations, perhaps as a consequence of uncertainty regarding management options. The importance of this unmet need is highlighted by the inclusion of fatigue among the James Lind Alliance's top 10 research priorities.³⁰ Fostering active questioning about fatigue during clinical encounters is an important first step.

Despite investigation, a specific cause of fatigue often cannot be identified. This knowledge gap makes IBD-related fatigue an important area of interest for future research, with the potential to improve our understanding of its underlying mechanisms and to support the development of novel targeted treatments. Currently evidence from RCTs is insufficient to support any single treatment approach. This highlights an opportunity to prioritize IBD-related fatigue as a research focus, particularly in relation to alerting medications. If successful, these treatments can have a palpable and direct improvement in patients' quality of life.

Conclusion

Regular use of validated assessment tools for fatigue will provide insight into our understanding of how the landscape of fatigue evolves over time and help evaluate the effectiveness of emerging therapies.

In clinical practice, proactive identification of fatigue, targeted investigations for reversible causes, and ongoing reassessments form the basis for practical steps to managing IBD-related fatigue.

Correspondence

Yaa Danso, MBBS, MRCP, IBD Research Fellow
Email: yaa.danso@nhs.net

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References

1. Danso Y, Hart AL, Alexander JL, Moulton CD. Fatigue in inflammatory bowel disease: a practical guide for gastroenterology clinicians. *Frontline Gastroenterology*. Published Online First: 05 August 2025. doi:10.1136/flgastro-2024-103035
2. Farrell D, McCarthy G, Savage E. Self-reported symptom burden in individuals with inflammatory bowel disease. *J Crohns Colitis*. 2016;10(3):315-322. doi:10.1093/ecco-jcc/jjv218
3. Hawthorne AB, Christiansen P, Arnott I, Cummings JRF, Dobson L, Kent A, et al. Determining the care quality perception gap between patients and service providers: comparative analysis of 2019 and 2023 UK IBD benchmarking data from more than 26,000 adult patients and 154 IBD services. *J Crohns Colitis*. 2026;20(3):jjag005. doi:10.1093/ecco-jcc/jjag005
4. Czuber-Dochan W, Norton C, Bassett P, Berliner S, Bredin F, Darvell M, et al. Development and psychometric testing of the IBD Fatigue (IBD-F) questionnaire. *J Crohns Colitis*. 2014;8(11):1398-1406.
5. Regueiro M, Su S, Vadharaya A, Zhou X, Durand F, Stassek L, et al. Psychometric evaluation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) in adults with moderately to severely active Crohn's disease. *Qual Life Res*. 2025;34(2):509-521. doi:10.1007/s11136-024-03829-3
6. Cella D, de la Loge C, Fofana F, Guo S, Ellis A, Fleurinck C, et al. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale in patients with axial spondyloarthritis: psychometric properties and clinically meaningful thresholds for interpretation. *J Patient Rep Outcomes*. 2024;8(1):92. doi:10.1186/s41687-024-00769-x
7. Patarca R. Cytokines and chronic fatigue syndrome. *Ann N Y Acad Sci*. 2001;933:185-200. doi:10.1111/j.1749-6632.2001.tb05824.x

8. Vogelaar L, de Haar C, Aerts BR, Peppelenbosch MP, Timman R, Hanssen BE, et al. Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters. *Clin Exp Gastroenterol*. 2017;10:83–90. doi:10.2147/CEG.S123942
9. Thong MSY, Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. *Curr Treat Options Oncol*. 2020;21(2):17. doi:10.1007/s11864-020-0707-5. Erratum in: *Curr Treat Options Oncol*. 2022;23(3):450–451. doi:10.1007/s11864-021-00916-2
10. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut–brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203–209. Erratum in: *Ann Gastroenterol*. 2016;29(2):240.
11. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*. 2004;43(4):678–683. doi:10.1016/j.jacc.2003.07.050
12. Norton C, Czuber-Dochan W, Bassett P, Berliner S, Bredin F, Darvell M, et al. Assessing fatigue in inflammatory bowel disease: comparison of three fatigue scales. *Aliment Pharmacol Ther*. 2015;42(2):203–211. doi:10.1111/apt.13255
13. van Langenberg DR, Della Gatta P, Warmington SA, Kidgell DJ, Gibson PR, Russell AP. Objectively measured muscle fatigue in Crohn's disease: correlation with self-reported fatigue and associated factors for clinical application. *J Crohns Colitis*. 2014;8(2):137–146. doi:10.1016/j.crohns.2013.07.006
14. Foster JA, McVey Neufeld KA. Gut–brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. 2013;36(5):305–312. doi:10.1016/j.tins.2013.01.005
15. Czuber-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. *J Crohns Colitis*. 2014;8(8):835–844. doi:10.1016/j.crohns.2014.01.004
16. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev*. 2015;22:23–36. doi:10.1016/j.smr.2014.10.001
17. De Pasquale C, El Kazzi M, Sutherland K, Shriane AE, Vincent GE, Cistulli PA, et al. Sleep hygiene – what do we mean? A bibliographic review. *Sleep Med Rev*. 2024;75:101930. doi:10.1016/j.smr.2024.101930
18. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011;377(9768):823–836. doi:10.1016/S0140-6736(11)60096-2
19. Moulton CD, Jordan C, Hayee B, Chalder T. All-or-nothing behavior and catastrophic thinking predict fatigue in inflammatory bowel disease: a prospective cohort study. *Inflamm Bowel Dis*. 2024;30(10):1903–1906. doi:10.1093/ibd/izad193
20. Ford AC, Wright-Hughes A, Alderson SL, Ow PL, Ridd MJ, Foy R, et al. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10414):1773–1785. doi:10.1016/S0140-6736(23)01523-4
21. Drossman DA, Tack J, Ford AC, Szegedy E, Törnblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut–brain interaction): a Rome Foundation working team report. *Gastroenterology*. 2018;154(4):1140–1171. doi:10.1053/j.gastro.2017.11.279
22. Kent JM. SNRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet*. 2000;355(9207):911–918. doi:10.1016/S0140-6736(99)11381-3
23. Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, McGuire H, et al. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute- phase treatment of adults with depression: systematic review and meta- analysis. *CNS Drugs* 2010;24(1):35–53. doi:10.2165/11319480-000000000-00000
24. Taylor D, Barnes TRE, Young A. The maudslay prescribing guidelines in psychiatry. Wiley- Blackwell; 2021. doi:10.1002/9781119870203
25. Kunz D, Dauvilliers Y, Benes H, García-Borreguero D, Plazzi G, Seboek Kinter D, et al. Long-term safety and tolerability of daridorexant in patients with insomnia disorder. *CNS Drugs*. 2023;37(1):93–106. doi:10.1007/s40263-022-00980-8
26. Gao T, Wang Z, Dong Y, Cao J, Lin R, Wang X, et al. Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice. *J Pineal Res*. 2019;67(1):e12574. doi:10.1111/jpi.12574
27. Flynn Pharma Ltd. Circadin 2 mg prolonged-release tablets – summary of product characteristics (SmPC). 2025 [Accessed 28 Apr 2025]. Available from: <https://www.medicines.org.uk/emc/product/2809/smpe>.
28. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*. 2008;10(3):329–336. doi:10.31887/DCNS.2008.10.3/dnutt
29. Modafinil (Provigil): increased risk of congenital malformations if used during pregnancy. GOV.UK. 2020 [Accessed 28 Apr 2025]. Available from: <https://www.gov.uk/drug-safety-update/modafinil-provigil-increased-risk-of-congenital-malformations-if-used-during-pregnancy>.
30. Hart AL, Lomer M, Verjee A, Kemp K, Faiz O, Daly A, et al. What are the top 10 research questions in the treatment of inflammatory bowel disease? A priority setting partnership with the James Lind Alliance. *J Crohns Colitis*. 2017;11(2):204–211. doi:10.1093/ecco-jcc/jjw144