

# LOOKING TO THE FUTURE:

## Research into fatigue in IBD



**DR CALUM MOULTON**

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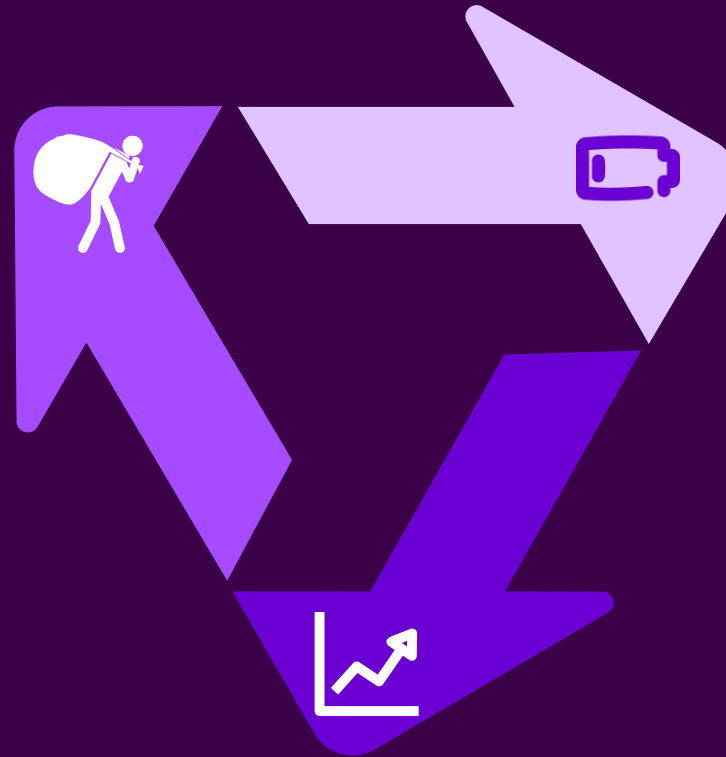


Disclosures: Fees from AbbVie, Dr Falk, Ferring, Lilly and Takeda for educational talks



# RECAP

Fatigue is often the most burdensome symptom for patients with IBD<sup>1</sup>



Even in IBD remission, around 4 in 10 have pervasive fatigue

Fatigue predicts increased healthcare utilisation<sup>2</sup>

1. Farrell D, et al. *J Crohns Colitis*. 2016;10:315–22; 2. Ananthakrishnan AN, et al. *Crohns Colitis 360*. 2023;5:1–9.



# **PREVIOUS TRIALS IN IBD-RELATED FATIGUE**



## INFLAMMATORY BOWEL DISEASE



### Effect of 5-Hydroxytryptophan on Fatigue in Quiescent Inflammatory Bowel Disease: A Randomized Controlled Trial

Marie Truysens,<sup>1,2,3</sup> Triana Lobatón,<sup>1,2</sup> Marc Ferrante,<sup>4,5</sup> Peter Bossuyt,<sup>6</sup> Séverine Vermeire,<sup>4,5</sup> Lieven Pouillon,<sup>6</sup> Pieter Dewint,<sup>7,8</sup> Anneline Cremer,<sup>9</sup> Harald Peeters,<sup>10</sup> Guy Lambrecht,<sup>11</sup> Edouard Louis,<sup>12</sup> Jean-François Rahier,<sup>13</sup> Olivier Dewit,<sup>14</sup> Vinciane Muls,<sup>15</sup> Tom Holvoet,<sup>2,16</sup> Liv Vandermeulen,<sup>17</sup> Anneleen Peeters,<sup>2</sup> Gerard Bryan Gonzales,<sup>1,18</sup> Simon Bos,<sup>1,3</sup> Debby Laukens,<sup>1,3,§</sup> and Martine De Vos<sup>1,§</sup>



Despite increasing serotonin levels, 5-hydroxytryptophan did not modulate IBD fatigue

Very high dose thiamine showed initial promise as a treatment for fatigue in IBD...



RANDOMISED CLINICAL TRIAL

### Randomised clinical trial: high-dose oral thiamine versus placebo for chronic fatigue in patients with quiescent inflammatory bowel disease

[Palle Bager](#) ✉, [Christian Lodberg Hvas](#), [Charlotte Lock Rud](#), [Jens Frederik Dahlerup](#)

First published: 18 November 2020 | <https://doi.org/10.1111/apt.16166>



Randomized Controlled Trial > [Scand J Gastroenterol.](#) 2022 Jan;57(1):37–43.

doi: 10.1080/00365521.2021.1983640. Epub 2021 Sep 30.

### Long-term maintenance treatment with 300 mg thiamine for fatigue in patients with inflammatory bowel disease: results from an open-label extension of the TARIF study

[Palle Bager](#)<sup>1</sup>, [Christian Lodberg Hvas](#)<sup>1</sup>, [Charlotte Lock Rud](#)<sup>1</sup>, [Jens Frederik Dahlerup](#)<sup>1</sup>

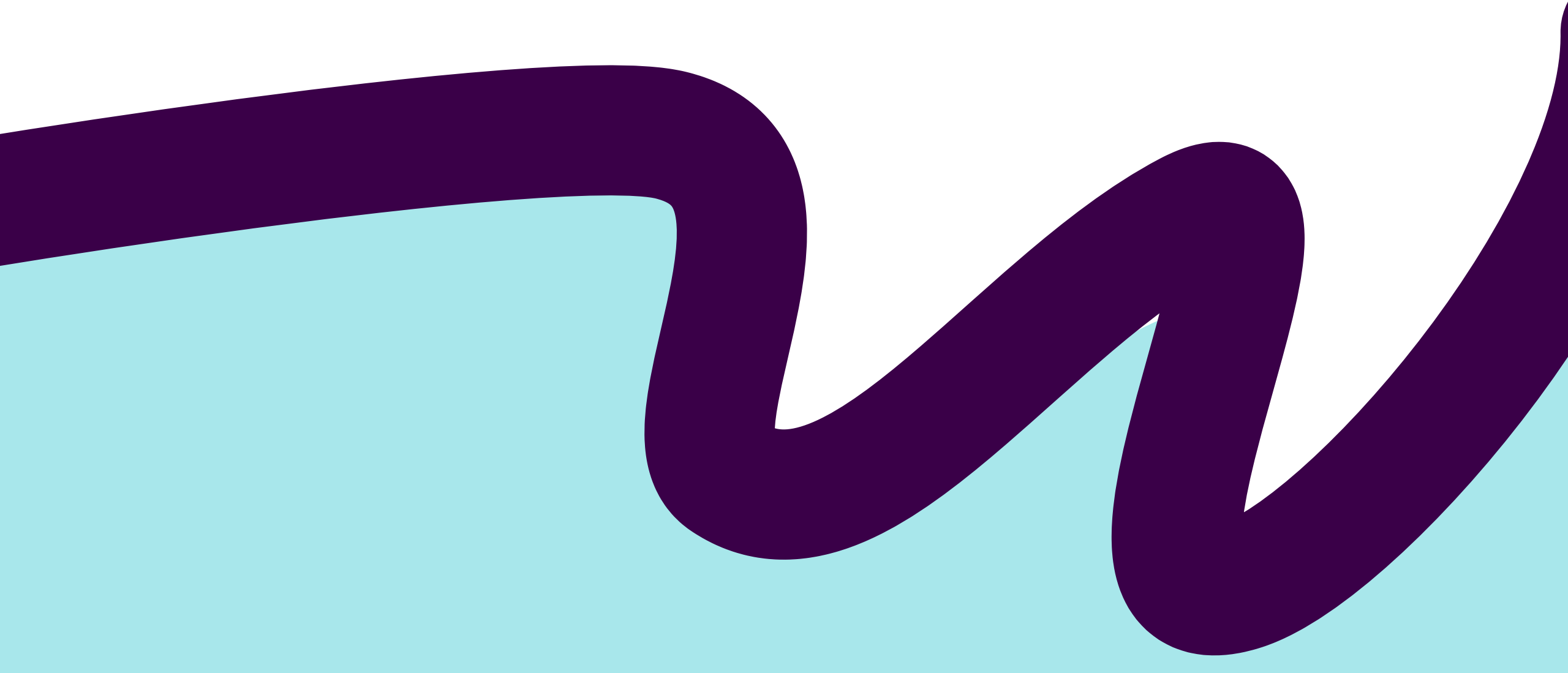
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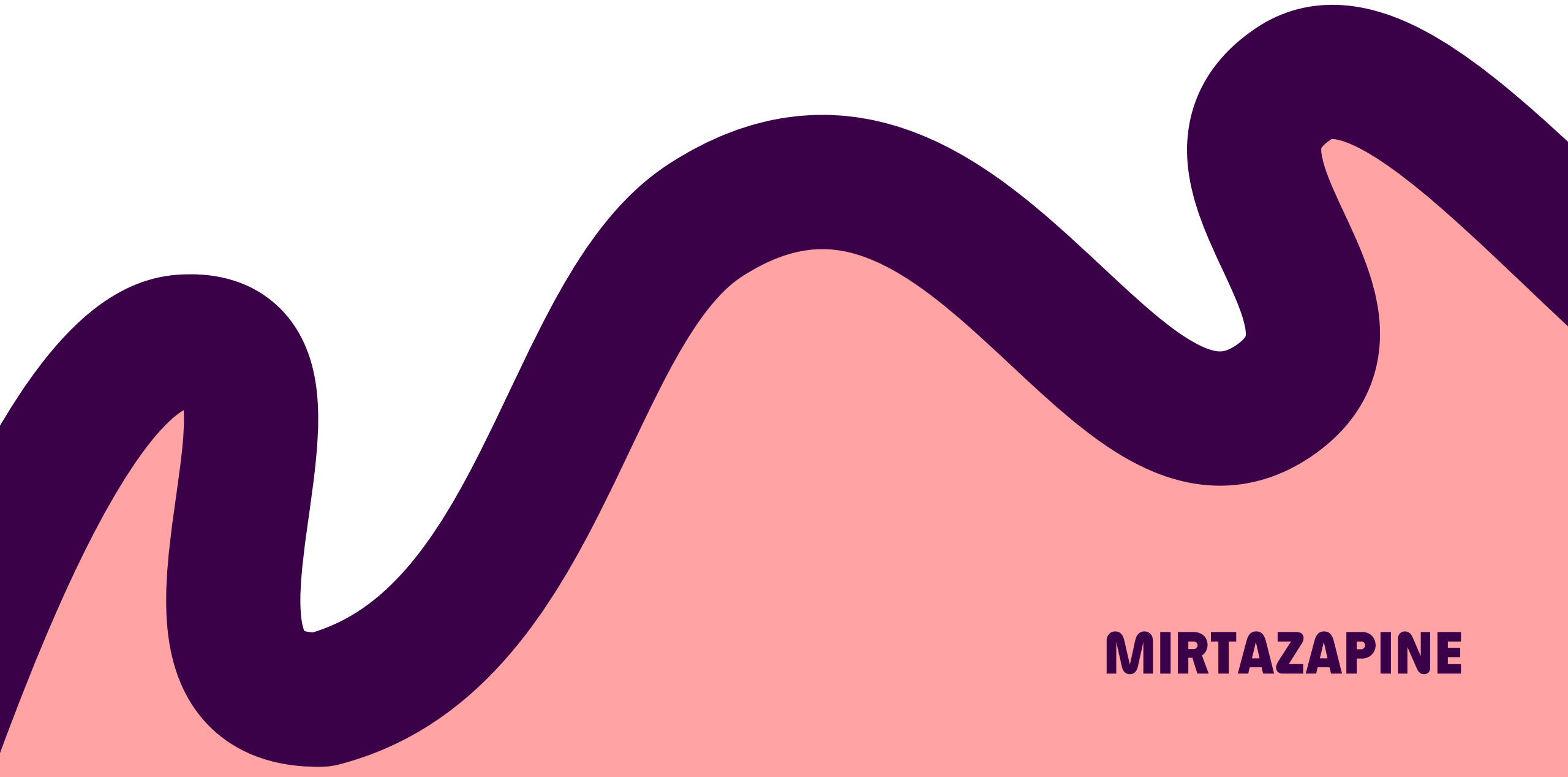
PMID: 34592862 DOI: [10.1080/00365521.2021.1983640](https://doi.org/10.1080/00365521.2021.1983640)

...but this was not seen in the follow-up study



# RECENT PROMISING RESEARCH





**MIRTAZAPINE**

# MIRTAZAPINE



## Trial of Mirtazapine for Depression in IBD (MDIBD)

**ClinicalTrials.gov ID** ⓘ NCT06309472

**Sponsor** ⓘ King's College London

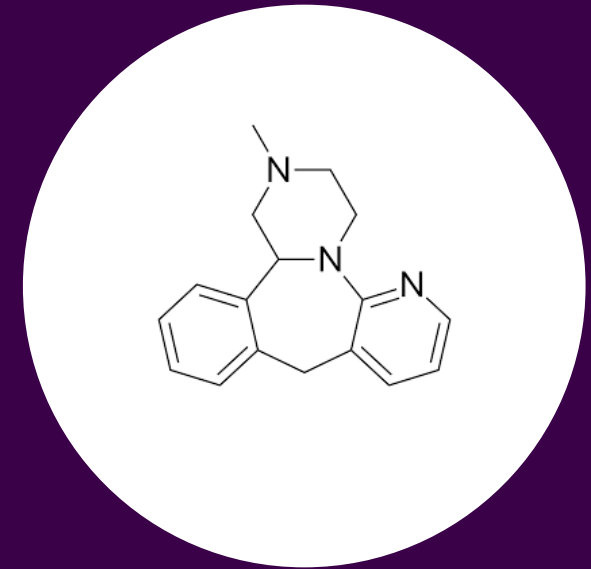
**Information provided by** ⓘ Calum Moulton, King's College London (Responsible Party)

**Last Update Posted** ⓘ 2024-08-22



# MIRTAZAPINE

- **Tetracyclic antidepressant**
- Can be **co-prescribed alongside other antidepressants**
- Some evidence in IBS, and **may help with early satiation** (feeling of fullness) and **chronic nausea/vomiting<sup>2</sup>**
- **Main side effects are weight gain and sedation:** these can be desirable



# WHY MIRTAZAPINE?

1. Low risk of diarrhoea

2. Anti-sickness effects

3. Improves insomnia

4. Doesn't increase risk of GI bleeding

5. Low risk of sexual dysfunction

6. Very good intestinal absorption



# MD-IBD: STUDY OVERVIEW



**DESIGN:** a feasibility, placebo-controlled, double-blind, randomised controlled trial (non-CTIMP)



# MD-IBD: STUDY OVERVIEW



**DESIGN:** a feasibility, placebo-controlled, double-blind, randomised controlled trial (non-CTIMP)



**AIM:** test whether it is feasible to carry out a trial of mirtazapine vs placebo for depression in patients with IBD



**POPULATION:** adults with Crohn's Disease or Ulcerative Colitis (inactive or stably active) AND major depression



**RECRUITMENT:** patients identified from IBD clinics across 4 hospitals – recruitment and follow-ups now complete



**FUNDING:** NIHR Advanced Fellowship



# MD-IBD: PRELIMINARY RESULTS



- **76** patients recruited
  - **97%** had **severe fatigue**
  - **93%** had **significant sleep disruption**



- **No serious adverse reactions**



- **Strong** signal of benefit on **depression and anxiety**



- **Small** signal of benefit on **fatigue**



- Findings need replication in a larger trial





**DARIDOREXANT**

# DARIDOREXANT

- **Orexins** normally help to **keep the brain awake**
- Daridorexant **blocks the orexin receptors in the brain**
- This **helps the brain to “switch off”**
- Daridorexant is a **licensed treatment for insomnia**
- Usually **well tolerated** with very **low risk of dependence**



# DARIDOREXANT EXPERIENCE AT ST MARK'S



10 patients with IBD treated with daridorexant 50mg at night



Patients completed the Pittsburgh Sleep Quality Index (PSQI) at baseline and after 3 months of daridorexant



Scores on the PSQI 8/21 indicate poor sleep quality

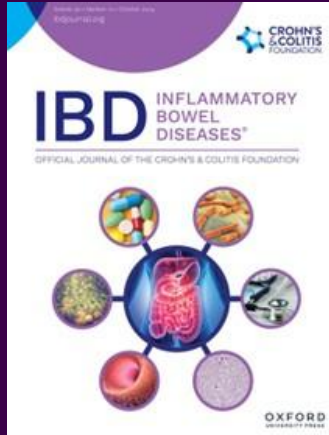


Scores improved significantly from 16.7 at baseline to 10.9 at follow-up ( $p < 0.001$ )



Daridorexant was well tolerated by all patients





*Inflammatory Bowel Diseases*, 2024, **30**, 1903–1906



<https://doi.org/10.1093/ibd/izad193>

Advance access publication 24 August 2023

**Brief Report - Clinical**



# All-or-Nothing Behavior and Catastrophic Thinking Predict Fatigue in Inflammatory Bowel Disease: A Prospective Cohort Study

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## Lay Summary

Patients with inflammatory bowel disease (IBD) often report fatigue. However, the reasons for this are poorly understood. In this study of people with IBD, we demonstrate that all-or-nothing behavior (being very active then needing to resting a while) and catastrophic thinking (making very negative assumptions about outcomes) both predict worsening in fatigue over time.

**Key Words:** fatigue, prospective, all-or-nothing behavior, catastrophic thinking, chronic fatigue syndrome



# 66 99

**I WOULD ALWAYS USE TO DO TOO MUCH, PUSH THROUGH AND THEN 'CRASH AND BURN', EXPERIENCING HUGE BOUTS OF FATIGUE AND TAKING TIME OFF WORK. NOW, I AM MORE REALISTIC WITH MY LIFE AND PLANS, STILL HAVING FUN AND FACTORING IN REST.**

**Sophie**, living with Crohn's Disease



# AVOID “ALL-OR-NOTHING” ACTIVITY PATTERNS

“All-or-nothing” behaviour in IBD is common

Patients may then experience “boom and bust” in fatigue

Instead, advise **regular** activity, increasing in a **graded** fashion



[crohnsandcolitis.org.uk/exercise](https://crohnsandcolitis.org.uk/exercise)



**I WALK OR RUN DEPENDING UPON HOW I FEEL. MY TIP IS NOT TO PUT PRESSURE ON YOURSELF IF YOU ARE IN A FLARE-UP. MY OTHER TIP IS TO FIND AN ACTIVITY YOU ENJOY, AS YOU ARE MORE LIKELY TO DO IT.**

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**WHATEVER YOU DO IS BETTER THAN DOING NOTHING. KEEPING FIT HAS HELPED ME TO FIGHT MY CONDITION AND LEAD A FULL LIFE. SOMETIMES THE HARDEST STEP IS THE FIRST ONE. YOU'VE GOT THIS.**



# **FUTURE RESEARCH**

**MODAFINIL**





# Modafinil for severe fatigue in Inflammatory Bowel Disease: a feasibility randomised controlled trial

## USING MODAFINIL AS A TREATMENT FOR SEVERE FATIGUE IN INFLAMMATORY BOWEL DISEASE

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**WE HOPE THIS TRIAL WILL BEGIN A NEW DAWN OF MEDICATION TREATMENTS FOR FATIGUE IN IBD.**

Dr Calum Moulton, King's College London

### WHAT THE RESEARCHERS WILL LOOK AT?

Fatigue is a common symptom of Crohn's and Colitis. It affects half the people living with these conditions. Although fatigue is common, there are not many medicines that can treat it. Researchers think that a medicine called modafinil could help treat fatigue.

Modafinil is currently used to treat narcolepsy. This is a condition that affects a person's ability to stay awake. Modafinil works by increasing the amount of dopamine in the brain. Dopamine is a chemical that is naturally found in the body and helps control energy levels.

This research is a "feasibility study". This means it will test whether it is possible or worth doing a larger version of the study. This type of study is needed because there have been no previous studies of modafinil in people living with Crohn's or Colitis.

Researchers will recruit adults who experience fatigue as part of Crohn's or Colitis. These adults will be asked to take one tablet twice a day for 12 weeks. This tablet will either be modafinil or a placebo. A placebo is a substance that looks the same as the treatment but does not have any medicine in it. The patients will not know which tablet they have been given and nor will the researchers. This is called a randomised controlled trial.

Researchers will measure:

- How many people join the study
- How many complete the treatment
- How many of the prescribed tablets people take
- How acceptable people felt the trial was
- They will ask people about their fatigue, mental health, and symptoms at 6 and 12 weeks during the trial.

The researchers will use the results of these measures to work out if it is possible to do a larger scale study.

### WHAT THE RESEARCHERS THINK THIS COULD THIS MEAN FOR PEOPLE WITH INFLAMMATORY BOWEL DISEASE?

The researchers hope this study will lead to larger clinical trials of using modafinil to treat fatigue. If successful, they hope this will lead to modafinil being widely used as an effective treatment for people living with fatigue and Crohn's or Colitis. They also think it will lead to more research into new treatments for fatigue.

**Who is leading this research:** Dr Calum Moulton, King's College London

**Our funding:** £149,679.42

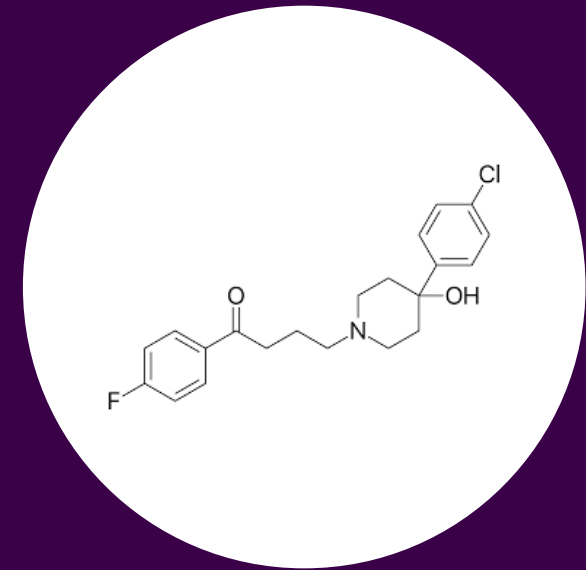
**Duration:** 24 months

**Official title of application:** Modafinil for severe fatigue in Inflammatory Bowel Disease: A placebo-controlled, feasibility randomised controlled trial.



# MODAFINIL

- Stimulant: weak dopamine reuptake inhibitor
- Rapid-acting, then wears off later in the day
- Start 100mg once daily, then increase it to 100mg morning and midday; maximum dose 400mg a day
- Can be combined with antidepressants
- Licensed for narcolepsy



# MODAFINIL STUDY OVERVIEW



**DESIGN:** a feasibility, placebo-controlled, double-blind, randomised controlled trial



# MODAFINIL STUDY OVERVIEW



**DESIGN:** a feasibility, placebo-controlled, double-blind, randomised controlled trial



**AIM:** test whether it is feasible to carry out a trial of modafinil vs placebo for severe fatigue in patients with IBD



**RECRUITMENT:** patients identified from IBD clinics (use IBD Fatigue score  $\geq 11/20$  if possible) and referred to study team



**TARGET SAMPLE SIZE:** 70 patients from four hospitals in London



**FUNDING:** Crohn's & Colitis UK and Jon Moulton Foundation



## Project information

**Organ:** Intestinal

**Disorder:** IBD (Crohn's disease and ulcerative colitis)

**Project title:** Modafinil for severe fatigue symptoms in chronic inflammatory bowel disease (IBD): a multicenter, randomized, double-blind, placebo-controlled, clinical trial (MODIFI-IBD study)

**Project leader:** Dr. Marjolein Duijvestein

**Institution:** Radboud UMC

**Started in:** January 2026

**Duration:** 1.5 years

**Status:** Ongoing

### Why is this research important?

In the Netherlands, tens of thousands of people have [Crohn's disease](#) or [ulcerative colitis](#) (together also called IBD). Many people with IBD suffer from severe fatigue. In fact, it is the most frequently mentioned complaint. This persistent fatigue strongly affects their daily lives. Unfortunately, there is no good treatment for this problem yet.

Modafinil is a drug that helps against fatigue and drowsiness. It has been used for some time in people with the sleeping sickness narcolepsy. Previous research with a small group of people suggests that modafinil may also help with fatigue in IBD. Researchers at Radboud UMC are now going to test the drug in a larger group of people with IBD. Modafinil would then be a new and convenient treatment for fatigue in IBD. This study is a first step and may later also help with other MDL conditions in which fatigue plays a role.



# MODAFINIL

- The trial is open to patients at King's College Hospital, Guy's and St Thomas' Hospital, St Mark's Hospital and Imperial College Healthcare. If the trial is successful, we will apply to do a bigger trial that will cover more sites.
- Modafinil currently not available on the NHS unless you have narcolepsy.
- If the trials in IBD are successful, we hope to have modafinil relicensed for fatigue in IBD in the coming years.



# TAKEAWAYS

- Avoid screentime 1 hour before bed; minimise alcohol intake and avoid caffeine 6 hours before bed
- Ensure a consistent waking time (even if nighttime sleep has been poor), maintain sunlight exposure during the day, and avoid daytime sleep as much as possible
- If sleep is still poor, consider making an appointment with your GP to discuss medications, particularly if you experience low mood or reduced enjoyment
- To help manage energy levels, avoid "overdoing it" on better days - instead, gradually increase levels of physical activity over time
- Interested in Crohn's & Colitis UK's research? Find out more at: [crohnsandcolitis.org.uk/our-work/research-and-evidence](https://crohnsandcolitis.org.uk/our-work/research-and-evidence)

