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INFLAMMATORY BOWEL DISEASE

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

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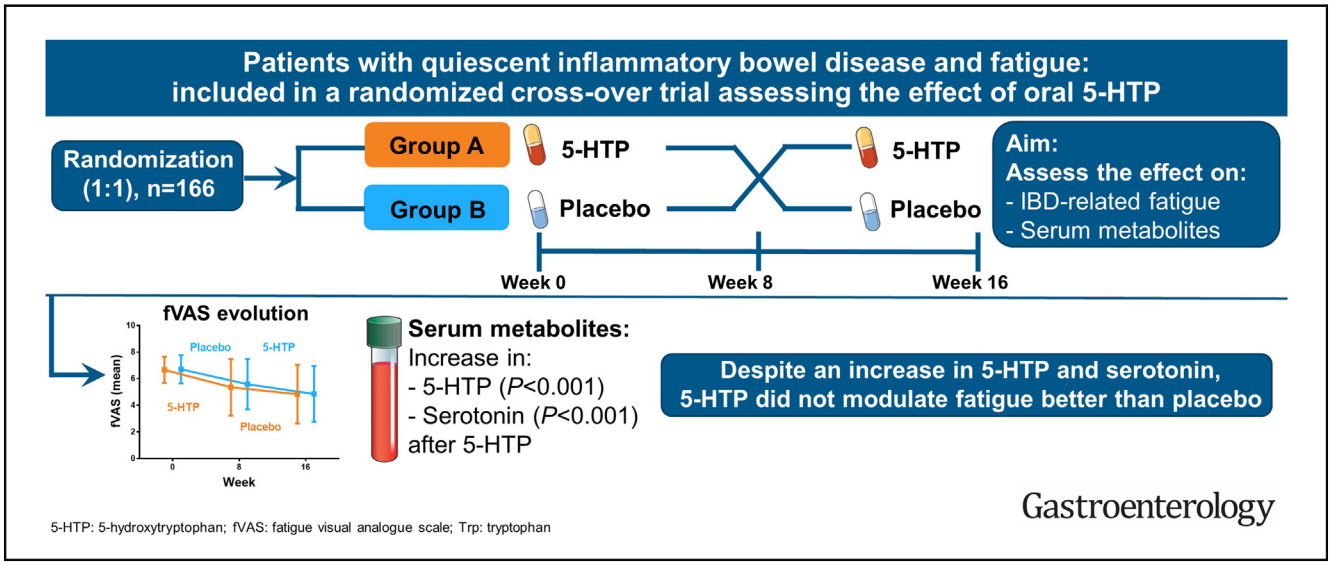

See editorial on page 1164.

BACKGROUND & AIMS: Fatigue is highly prevalent among patients with inflammatory bowel disease (IBD), and only limited treatment options are available. Based on the hypothetical link between low serum tryptophan concentrations and fatigue, we determined the effect of 5-hydroxytryptophan supplementation on fatigue in patients with inactive IBD. **METHODS:** A multicenter randomized controlled trial was performed at 13 Belgian hospitals, including 166 patients with IBD in remission but experiencing fatigue, defined by a fatigue visual analog scale (fVAS) score of $\geq$5. Patients were treated in a crossover manner with 100 mg oral 5-hydroxytryptophan or placebo twice daily for 2 consecutive periods of 8 weeks. The primary end point was the proportion of patients reaching a $\geq$20% reduction in fVAS after 8 weeks of intervention. Secondary outcomes included changes in serum tryptophan metabolites, Functional Assessment of Chronic Illness Therapy Fatigue scale, and scores for depression, anxiety, and stress.

The effect of the intervention on the outcomes was evaluated by linear mixed modeling. **RESULTS:** During 5-hydroxytryptophan treatment, a significant increase in serum 5-hydroxytryptophan (estimated mean difference, 52.66 ng/mL; 95% confidence interval [CI], 39.34–65.98 ng/mL; $P < .001$) and serotonin (3.0 ng/mL; 95 CI, 1.97–4.03 ng/mL; $P < .001$) levels was observed compared with placebo. The proportion of patients reaching ≥20% reduction in fVAS was similar in placebo- (37.6%) and 5-hydroxytryptophan (35.6%)-treated patients ($P = .830$). The fVAS reduction (−0.18; 95% CI, −0.81 to 0.46; $P = .581$) and Functional Assessment of Chronic Illness Therapy Fatigue scale increase (0.68; 95% CI, −2.37 to 3.73; $P = .660$) were both comparable between 5-hydroxytryptophan and placebo treatment as well as changes in depression, anxiety, and stress scores. **CONCLUSIONS:** Despite a significant increase in serum 5-hydroxytryptophan and serotonin levels, oral 5-hydroxytryptophan did not modulate IBD-related fatigue better than placebo. (Trial Registration: Belgian Federal Agency for Medication and Health Products, EudraCT number: 2017-005059-10 and ClinicalTrials.gov: NCT03574948, https://clinicaltrials.gov/ct2/show/NCT03574948.)

Keywords: Crohn's Disease; Ulcerative Colitis; Exhaustion; Neurobehavior.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Fatigue is highly prevalent in patients with inflammatory bowel disease. Reduced serum tryptophan has been linked to fatigue in inactive inflammatory bowel disease. The aim was to determine the effect of 5-hydroxytryptophan on inflammatory bowel disease–related fatigue.

NEW FINDINGS

A significant increase in 5-hydroxytryptophan and serotonin serum levels was observed during 5-hydroxytryptophan treatment. There was a fatigue reduction throughout the study; however, this was comparable between 5-hydroxytryptophan and placebo.

LIMITATIONS

Mainly patients with Crohn's disease were included.

IMPACT

This crossover, randomized controlled trial showed no effectiveness of oral supplementation with 5-hydroxytryptophan in the treatment of inflammatory bowel disease–related fatigue.

Fatigue is defined as exhaustion that is disproportionate to exertion and is not alleviated by rest.[1] Its prevalence in patients with inflammatory bowel disease (IBD) ranges from 72% during active disease to 47% during disease remission.[2] Despite the progress in controlling intestinal inflammation, fatigue remains an unmet clinical need, leading to reduced quality of life,[3,4] absenteeism, and presenteeism.[5,6]

The pathogenesis of fatigue is poorly understood and is multifactorial. Factors such as inflammation, psychological comorbidities, metabolic alterations, micronutrient deficiencies, and sleep disturbances are thought to play a role.[2,3] Therapeutic options for IBD-related fatigue are limited, with some evidence for psychotherapy,[7] thiamine treatment,[8] and physical activity.[9] In addition, evidence of its relationship with depression and anxiety, which are more prevalent among patients with IBD, remains elusive.[10–12]

An interesting pathway that may contribute to neurobehavioral problems is controlled by tryptophan (Trp) metabolism (Supplementary Figure 1), which is significantly modulated during IBD pathogenesis.[13–15] Patients with active IBD exhibit low serum Trp levels mainly due to inflammation-induced upregulation of indoleamine 2,3-dioxygenase 1 (IDO1), which is the rate-limiting enzyme catalyzing Trp to kynurenine conversion, thus shifting Trp metabolism to the kynurenine pathway.[16] Even when patients reach disease remission, IDO1 expression has been shown to remain high.[17]

Trp and kynurenine can pass the blood-brain barrier, after which a set of enzymes expressed in astrocytes and microglia can lead to the local formation of neuroactive kynurenines such as quinolinic acid and kynurenic acid.[15] Quinolinic acid, an agonist of *N*-methyl-D-aspartate receptors, can induce neurotoxic effects and is hypothesized to play a role in the pathophysiology of psychiatric and neurodegenerative disorders.[15,18] In contrast, kynurenic acid is considered neuroprotective, acting as an antagonist of *N*-methyl-D-aspartate receptors.[18] Increased quinolinic acid and decreased levels of kynurenic acid have been reported in the brain and cerebrospinal fluid of patients with depression.[15] However, data on these metabolites in patients with IBD are conflicting, with some studies reporting higher quinolinic acid and lower kynurenic acid serum levels[19] and another study reporting a positive correlation between kynurenic acid and the degree of intestinal inflammation.[20] Moreover, besides the overexpression of IDO1, little is known about the activation and expression of other enzymes of the kynurenine pathway in IBD.[15]

The Trp-to-serotonin pathway is another potential key player given that dysregulation has been reported in conditions with heightened fatigue perception,[21] although data are controversial.[7] Intestinal Trp hydroxylase converts Trp to 5-hydroxytryptophan (5-HTP), and both can pass the blood-brain barrier in contrast to serotonin itself.[22] Central

§ Authors share joint senior authorship.

Abbreviations used in this paper: 5-HTP, 5-hydroxytryptophan; AE, adverse event; CD, Crohn's disease; CI, confidence interval; DASS-21, Depression Anxiety and Stress Scale—21 items; DASS-A, Depression Anxiety and Stress Scale—Anxiety subscale; DASS-D, Depression Anxiety and Stress Scale—Depression subscale; DASS-S, Depression Anxiety and Stress Scale—Stress subscale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue scale; fVAS, fatigue visual analog scale; IBD, inflammatory bowel disease; IDO1, indoleamine 2,3-dioxygenase 1; IQR, interquartile range; ITT, intention to treat; LMM, linear mixed modeling; PP, per protocol; RCT, randomized controlled trial; Trp, tryptophan; UC, ulcerative colitis.

Most current article

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conversion to serotonin plays an important role in the regulation of mood, behavior, and cognitive function.[18,23] Finally, Trp is processed by the intestinal bacteria to indoles, which are ligands for the aryl hydrocarbon receptor, a transcription factor that regulates a variety of processes, including inflammatory responses. Anti-inflammatory effects in astrocytes mediated by dietary Trp metabolites were reported in an experimental model of multiple sclerosis, whereas in IBD, some evidence shows reduced aryl hydrocarbon receptor activity and Trp levels in feces.[24–26]

In rodent studies, serum Trp depletion reduced levels of Trp in the brain, with subsequently lower serotonin synthesis,[27,28] leading to alterations in mood and cognition.[29] The link between a biological deficiency of Trp and neurobehavioral abnormalities, such as fatigue, depression, and reduced well-being, has also been reported in humans.[30] Moreover, a correlation between fatigue and low serum Trp levels was shown in patients with cancer, patients with chronic renal insufficiency, and stroke survivors.[31–33]

Active IBD has been consistently associated with reduced serum Trp levels[16,19]; nonetheless, data on Trp levels during IBD in remission are more conflicting. In the study of Gupta et al,[16] Trp levels in patients with Crohn's disease (CD) in remission were comparable to the controls; however, only 4 patients were included. In the cohort of Nikolaus et al,[19] inactive CD was associated with lower Trp levels compared with the controls. Recently, Borren et al[34] showed reduced serum Trp levels relative to fatigue in quiescent IBD.

Treatment with 5-HTP has been extensively studied for depression, but mainly in smaller studies with heterogenous design, with different doses of 5-HTP, and differences in study duration.[35] There is currently less evidence for a positive effect of 5-HTP on fatigue; however, 1 randomized controlled trial (RCT) as well as a 90-day open-label study demonstrated significantly reduced fatigue, pain, and anxiety in patients with fibromyalgia.[36,37] The hypothesis of the current trial was that oral delivery of 5-HTP would modulate fatigue in patients with quiescent IBD. Treatment with 5-HTP was used instead of Trp to bypass a possible intestinal-specific Trp uptake disorder in patients with IBD[17,19] and to reinforce the serotonin pathway. Only patients with quiescent IBD were included to avoid the well-known influence of disease activity on IBD-related fatigue, for which the first step is optimizing IBD treatment.[38,39]

Materials and Methods

Trial Design

This double-blind, crossover RCT evaluated the effect of oral 5-HTP supplementation on fatigue in patients with IBD in remission. Enrollment occurred between December 2018 and November 2020 at 13 sites across Belgium (Supplementary Methods). Approval was obtained from the Ghent University Hospital Central Ethical Review Board (EC2018-0813, date: September 17, 2018) as well as from the Ethics Committees of all participating centers. A written informed consent form was acquired from each participant. All authors had access to the study data and reviewed and approved the final manuscript. The study was approved by the Belgian Federal Agency for Medication and Health Products, EudraCT number: 2017-005059-10.

Study Participants

The study population consisted of adult (aged ≥18 years) patients with CD or ulcerative colitis (UC) and experiencing fatigue. Fatigue was assessed using the fatigue visual analog scale (fVAS), which ranges from 0 to 10.[40] Patients could be considered for inclusion if they had a fVAS score of ≥5; this cutoff was selected based on previous studies.[41–43] Patients were eligible if they were treated with biologicals or immunosuppressants, or both, for ≥6 months with a stable dose over the last 3 months. All patients had to be in clinical remission over the last 3 months, and clinical remission was confirmed at enrollment based on the Simple Clinical Colitis Activity Index score of ≤2 for UC and the Harvey Bradshaw Index score of ≤4 for CD. At screening, patients had to have confirmed biochemical remission, defined by a C-reactive protein level of <10 mg/L and a fecal calprotectin level of <250 mg/kg.

Exclusion criteria were depression or other psychiatric comorbidities, use of antidepressant or neuroleptic agents, concomitant comorbidities (including cardiovascular disease, obstructive lung pathology, or neoplasia), a history of drug or alcohol abuse within 1 year before inclusion, documented anemia (hemoglobin <12 g/dL for women and <13 g/dL for men), deficiencies in iron (saturation index <20%), vitamin B_{12} (<148 pmol/L), or folic acid (<6 nmol/L), hypothyroidism (thyroid-stimulating hormone >4.20 mU/L), recent infection, oral corticosteroid use (in the last 8 weeks), pregnancy, breastfeeding, or surgery in the 12 weeks before the screening visit.

Study Treatment and Randomization

For the present trial, treatment with 5-HTP (Levotonine; Panpharma, Luitré, France) 100 mg, twice daily, was selected, based on previous studies performed with 5-HTP. In studies on depression, different doses of 5-HTP have been assessed, varying from 50 to 3000 mg/d.[35] In a more recent controlled trial, an antidepressant effect of 5-HTP was already seen at doses of 150 mg/d, whereas 300 mg of 5-HTP daily was efficient in reducing fatigue associated with fibromyalgia.[36] To minimize adverse events (AEs; possible increase in visceral hypersensitivity[44]) a dose of 200 mg/d was selected for the current trial. The study consisted of an 8-week treatment period with oral 5-HTP (100 mg) or placebo twice daily, followed by a crossover to the other treatment arm for an additional 8 weeks, without intermediate washout (Supplementary Figure 2). Patients were randomized to group A (5-HTP, followed by placebo) or group B (placebo, followed by 5-HTP) on a 1:1 ratio.

All medications were double-blinded. Randomization was performed by the University Hospital Ghent Clinical Trial Unit using www.randomization.com. The placebo and 5-HTP were packaged in identical plastic bottles by the Clinical Trial Unit. The containers were sequentially numbered and together with anonymized randomizations lists distributed to the participating hospitals.

Outcome Measures and Definitions

The study flowchart is shown in Supplementary Figure 2. The primary end point was an improvement of fatigue, defined

as an fVAS reduction of ≥20%.[43] The fVAS reduction was the difference in fVAS determined at week 8 and at enrollment for the first study period and between week 16 and week 8 for the second study period. Additionally, fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F), with scores ranging from 0 to 52 (inversely proportional to fatigue).[45]

Key secondary outcomes included depression, anxiety, and stress, which were evaluated by the Depression Anxiety and Stress Scale–21 items (DASS-21).[46] The DASS-21 subscales range from 0 to 42, and cutoff values of ≥10, ≥14, and ≥19 were used for the identification of anxiety (DASS-A), moderate to severe depression (DASS-D), and stress (DASS-S), respectively. Therapy adherence was assessed by counting returned capsules.

Adverse Events

AEs were assessed at each study visit and were defined as serious if they resulted in death (or were life-threatening), required hospitalization, or resulted in significant disability.

Serum Tryptophan Metabolites

At enrollment, week 8, and week 16, a blood sample was collected and immediately sent to Ghent University Hospital. The samples were centrifuged, and serum was stored at −80°C in the Bioresource Center Ghent (ID: BE 71067049). Trp metabolites (5-HTP, L-kynurenine, and serotonin) were determined at different time points using a targeted approach.

Analyses were performed at the University of Leuven Metabolomics Expertise Center. Internal standards were available for 5-HTP and kynurenine; thus, absolute concentrations could be reported. For serotonin, no internal standard was available, and approximate concentrations were reported. Samples were prepared by adding 545 μL methanol 100% and 5μL of standards mix to 50 μL of each serum sample. The solutions were kept at −80°C overnight, followed by centrifugation. The samples were dried and resuspended in 50 μL of 0.1% formic acid and transferred to mass spectrometry vials. Analysis was performed with a Vanquish UHPLC (Thermo Fisher Scientific, Bremen, Germany) equipped with a C-18 column (Acquity UPCL BEH 1.7 μm, 2.1 mm × 150 mm) coupled to a Q Exactive Orbitrap–Focus mass spectrometer (Thermo Fisher Scientific) operating in positive ion mode. The samples were analyzed in sequential order (per patient), and a standard mix was analyzed every 20 samples. Data collection was performed using Xcalibur software (Thermo Fisher Scientific). Outlier selection and removal was performed by Hotelling's T2 test, embedded in the SIMCA 14.0 software (Sartorius, Goettingen, Germany).

Statistical Analyses

SPSS 27.0 (IBM Armonk, NY) and GraphPad Prism (GraphPad Software Inc, San Diego, CA) software packages were used for statistical analysis and graphical representations of data. Data with a normal distribution and nonnormal distribution are presented with the mean and standard deviation or the median and interquartile range (IQR), respectively. To assess the primary end point, McNemar's test was used. The effect of the intervention on the outcomes was evaluated by linear mixed modeling (LMM), with the intervention, period, and their interaction (intervention × period) as fixed effects and study participant as a random effect. Differences were considered statistically significant when the P value was <.05. Intention to treat (ITT) and per-protocol (PP) principle were both applied for statistical analyses. In the ITT analysis, all patients meeting the above inclusion and exclusion criteria were included. A PP analysis was also performed, for which the following additional exclusion criteria were used: active disease (clinically and biochemically) at week 8, noncompliance (defined as an intake of <70% of pills), and study visits out of range. For the questionnaires, up to 3 days out of the window was accepted; for the samples, this was up to 7 days.

Results

Characteristics of the Study Population

The study screened 238 patients, of whom 175 were randomized (Figure 1). However, after review by the central study coordinator, 5 patients were not fatigued enough at enrollment, 3 patients had active disease, and 1 patient refused informed consent. These patients were excluded from the ITT and PP analyses, resulting in 166 analyzed patients. In total, 18 patients (10.8%) prematurely left the study, permitting to stop inclusion at 166 patients.

Baseline characteristics were comparable between both study groups (Table 1). The median percentage of capsules taken was 96.4% (IQR, 91.1%–99.1%) during placebo treatment and 96.4% (IQR, 90.2%–100%) during 5-HTP treatment. The compliance was comparable between both treatments (P = .707).

Evolution of Fatigue Scores

Intention-to-treat analysis. Both study groups had comparable baseline fVAS and FACIT-F (Table 2). The percentage of patients reaching ≥20% reduction in fVAS after 5-HTP (35.6% [53 of 149]) was similar to placebo (37.6% [56 of 149]; difference, 2.0%; 95% confidence interval [CI], −10.2% to 14.2%; P = .830). Furthermore, 5-HTP treatment was not associated with a significant reduction in fVAS (estimated mean difference, −0.18; 95% CI, −0.81 to 0.46; P = .581) or in FACIT-F (0.68; 95% CI, −2.37 to 3.73; P = .660) over placebo (Figure 2 and Table 2). Of note, a significant decrease in fVAS was found in both the placebo (–0.81, P < .001) and 5-HTP arms (–1.01, P = .003) throughout the study (Figure 3).

Per-protocol analysis. In the PP analysis, 118 patients could be evaluated at week 8 (group A, n = 57; group B, n = 61) and 108 patients at week 16 (group A, n = 53; group B, n = 55). Treatment with placebo and 5-HTP led to an estimated mean reduction in fVAS of −0.94 (95% CI, −1.36 to −0.53) and −0.97 (95 CI, −1.39 to −0.56), respectively. As in the ITT analysis, McNemar's test was applied for the assessment of the primary end point. For this pairwise analysis, 85 patients could be included. After 5-HTP treatment, 31 of 85 patients (36.5%) had a VAS reduction of ≥20%; after placebo treatment, this was the case in 39 of 85 patients (45.9%). The difference between both treatments was 9.4% (95% CI, −6.9% to 25.2%; P = .322); thus, in the PP analysis, the primary end point was

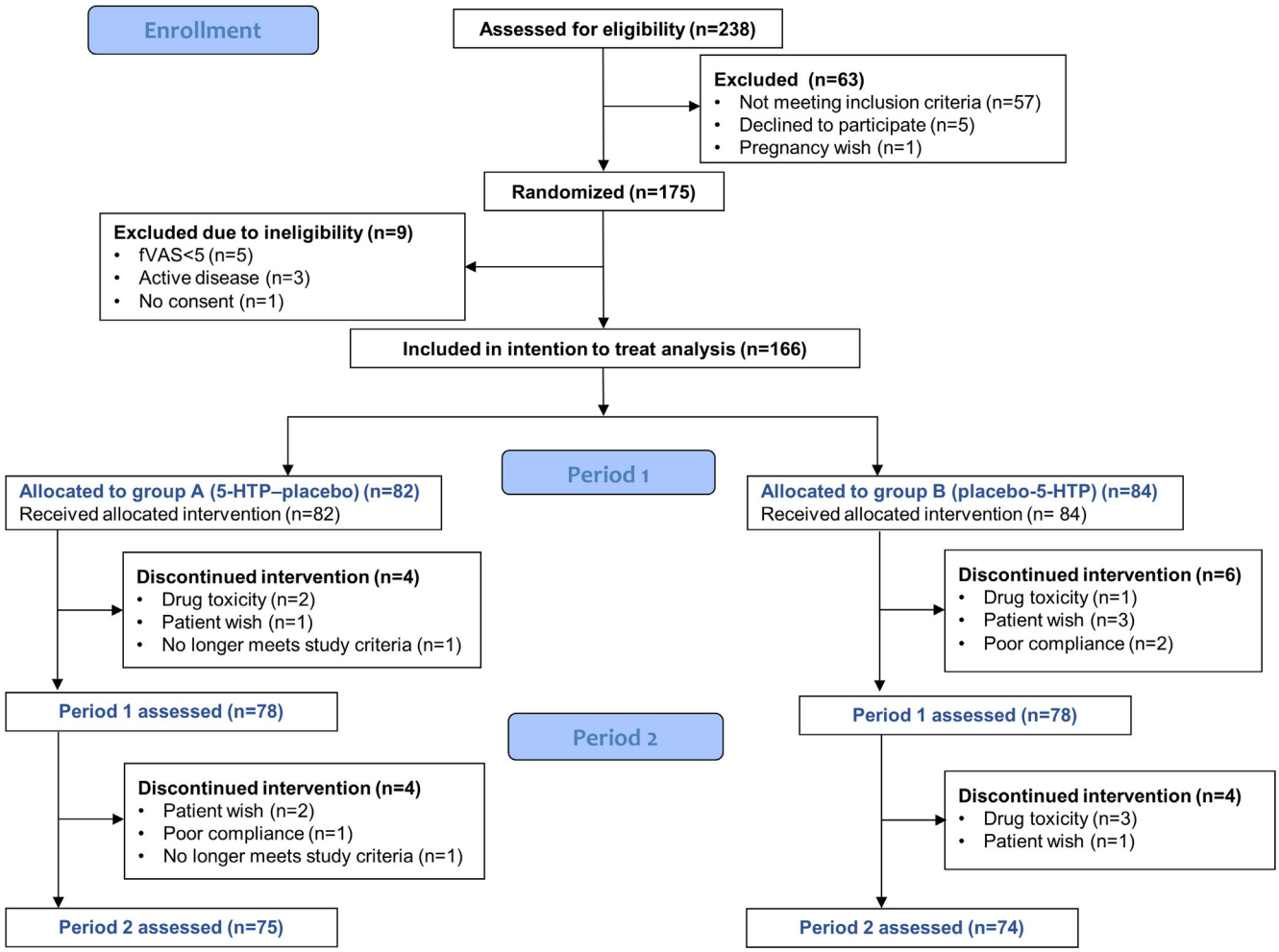

Figure 1. Consolidated Standards of Reporting Trials diagram.

also not met. Next, LMM reaffirmed that no differential effect of treatment on fVAS reduction (estimated mean difference, −0.03; 95% CI, −0.73 to 0.67; $P = .934$) or on FACIT-F (estimated mean difference, 0.84; 95% CI, −2.51 to 4.20; $P = .620$) could be noted.

Evolution of Other Patient-Reported Outcomes

Intention-to-treat analysis. At baseline, 44.5% of patients showed moderate to severe depressive symptoms (DASS-D ≥14) despite the exclusion of patients with clinical depression. Likewise, moderate to severe stress and anxiety symptoms were reported in 41.5% and 43.2% of patients based on DASS-S and DASS-A, respectively. An improvement of depression, stress, and anxiety scores was seen throughout the study; however, this was again comparable between placebo and 5-HTP treatment (Figure 3 and Table 2).

Per-protocol analysis. Treatment with 5-HTP and placebo led to a comparable estimated mean reduction in DASS-A (placebo: −1.54 [95% CI, −2.57 to −0.52], 5-HTP: −1.03 [95% CI, −2.06 to −0.01]), DASS-D (placebo: −1.69 [95% CI, −3.16 to −0.23], 5-HTP: −1.81 [−3.29 to −0.34]), and DASS-S (placebo: −2.63 [05% CI, −4.23 to −1.04], 5-HTP: −1.85 [95% CI, −3.45 to −0.24]). When the effect of treatment in an LMM was assessed, 5-HTP was not significantly associated with a reduction in DASS-A (0.51; 95% CI, −1.19 to 2.21; $P = .552$), DASS-S (0.79; 95% CI, −1.94 to 3.51; $P = .570$) or DASS-D (−0.12; 95% CI, −2.65 to 2.41; $P = .927$).

Assessment of Serum Tryptophan Metabolites

Baseline Trp metabolites were comparable between both study groups (Table 1). At baseline, there was no correlation between 5-HTP or serotonin levels and the severity of fatigue. Treatment with 5-HTP had no significant impact on serum kynurenine levels (Table 3). However, serum 5-HTP and serotonin levels significantly increased after 5-HTP treatment ($P < .001$ and $P < .001$, respectively). The evolution of serum 5-HTP and serotonin levels was similar in patients who reached a ≥20% reduction in fVAS compared with patients who did not (Figure 4).

Evolution Disease Activity and Adverse Events

Disease activity was monitored during each study visit by clinical activity indices and fecal calprotectin. Disease flare-ups were reported in 6 patients; all occurred during

Table 1. Baseline Patient Characteristics

Variables	Group A (5-HTP then placebo) (n = 82)	Group B (Placebo then 5-HTP) (n = 84)	Total (N = 166)
Female sex	45 (54.9)	49 (58.3)	94 (56.6)
Age, *y*	38.5 (29.8–45.0)	39.0 (29.3–48.0)	39.0 (29.8–46.0)
Disease duration, *y*	8.0 (5.0–13.0)	9.0 (5.0–17.0)	9.0 (5.0–15.0)
UC	22 (26.8)	24 (28.6)	46 (27.7)
SCCAI	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Disease location[a]			
E1	7 (31.8)	4 (16.7)	11 (23.9)
E2	7 (31.8)	9 (37.5)	16 (34.8)
E3	8 (36.4)	11 (45.8)	19 (41.3)
CD	60 (73.2)	60 (71.4)	120 (72.3)
Harvey Bradshaw Index	2.0 (1.0–2.8)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Disease location[a]			
L1	13 (21.7)	20 (33.3)	33 (27.5)
L1+L4	1 (1.7)	1 (1.7)	2 (1.7)
L2	16 (26.7)	10 (16.7)	26 (21.7)
L3	28 (46.7)	28 (46.7)	56 (46.7)
L3+L4	2 (3.3)	1 (1.7)	3 (2.5)
C-reactive protein, *mg/L*	1.1 (0.9–3.1)	1.3 (0.7–3.9)	1.2 (0.8–3.3)
Fecal calprotectin, *mg/kg*	22.5 (10.8–68.5)	30.0 (13.0–72.8)	27.5 (12–70.5)
Current treatment			
Immunosuppressant (IS)	9 (11)	8 (9.5)	17 (10.2)
Adalimumab (+/− IS)	21 (25.6)	20 (23.8)	41 (24.7)
Infliximab (+/− IS)	29 (35.4)	30 (35.7)	59 (35.5)
Vedolizumab (+/− IS)	13 (15.9)	19 (22.6)	32 (19.3)
Ustekinumab (+/− IS)	9 (11)	7 (8.3)	16 (9.6)
Tofacitinib	1 (1.2)	0	1 (0.6)
Previous biologicals, No.			
0	53 (64.6)	47 (56.0)	100 (60.2)
≥1	29 (35.4)	37 (44.0)	66 (39.8)
Baseline patient-reported outcomes			
fVAS	6.7 ± 1.0	6.7 ± 1.1	6.7 ± 1.0
FACIT-F	24.3 ± 7.2	24.5 ± 7.8	24.4 ± 7.5
DASS-A	9.1 ± 6.0	8.5 ± 7.2	8.8 ± 6.6
DASS-S	17.8 ± 11.2	17.2 ± 9.9	17.5 ± 10.5
DASS-D	11.4 ± 7.6	12.1 ± 8.5	11.8 ± 8.0
Baseline metabolites	(n = 79)	(n = 83)	(n = 162)
Kynurenine, *μmol/L*	3.0 (2.3–3.6)	2.9 (2.3–3.5)	2.9 (2.3–3.5)
5-HTP, *ng/mL*	66.5 (57.3–74.7)	66.1 (57.3–74.9)	66.4 (57.3–74.7)
Serotonin, *ng/mL*	7.0 (5.0–9.5)	7.1 (4.6–10.1)	7.1 (4.8–9.9)

NOTE. Values are mean ± standard deviation, median (IQR), or n (%).
SCCAI, Simple Clinical Colitis Activity Index.
[a]Disease location: Montreal classification.

the second study period (4 in group A, 2 in group B). The rate of other AEs was comparable between 5-HTP and placebo treatment (Supplementary Table 1). Serious AEs were identified in 3 patients. All 3 patients were hospitalized: 1 due to an elective knee replacement (during placebo), 1 due to insomnia (during 5-HTP), and 1 for severe gastroenteritis (during 5-HTP). All 3 patients recovered without sequelae.

Discussion

The current RCT in patients with IBD in clinical and biological remission demonstrated a clear reduction in fatigue measured throughout the study but independent of oral 5-HTP treatment. A similar result was found when assessing depression, anxiety, and stress.

Low serum Trp levels have been linked with IBD-related fatigue, which indicated a potential benefit of Trp

Table 2. Evolution of Patient-Reported Scores After Treatment

	Treatment		LMM analysis: 5-HTP vs placebo	
Variable	Placebo (n = 153)	5-HTP (n = 152)	Estimated mean difference (95% CI)	*P* value
fVAS	5.22 ± 2.08	5.12 ± 2.12		
Difference[a] in fVAS	−0.82 (−1.18 to −0.46)	−1.00 (−1.36 to −0.64)	−0.18 (−0.81 to 0.46)	.581
Week 8 vs week 0	−1.13 (−1.57 to −0.69)	−1.30 (−1.74 to −0.85)	−0.17 (−0.79 to 0.46)	.598
Week 16 vs week 8	−0.52 (−1.09 to 0.05)	−0.71 (−1.28 to −0.13)	−0.19 (−1.00 to 0.62)	.645
FACIT-F	30.53 ± 10.88	30.96 ± 9.85		
Difference[a] in FACIT-F	3.63 (1.93 to 5.32)	4.31 (2.60 to 6.01)	0.68 (−2.37 to 3.73)	.660
Week 8 vs week 0	4.62 (2.63 to 6.60)	5.01 (3.02 to 7.00)	0.40 (−2.41 to 3.20)	.781
Week 16 vs week 8	2.64 (−0.12 to 5.39)	3.61 (0.83 to 6.38)	0.97 (−2.94 to 4.88)	.626
DASS-A	6.64 ± 6.37	7.23 ± 6.21		
Difference[a] in DASS-A	−1.59 (−2.48 to −0.71)	−1.05 (−1.94 to −0.16)	0.54 (−0.99 to 2.07)	.484
Week 8 vs week 0	−0.83 (−1.96 to 0.31)	−1.09 (−2.23 to 0.05)	−0.27 (−1.87 to 1.34)	.745
Week 16 vs week 8	−2.36 (−3.73 to −0.99)	−1.01 (−2.38 to 0.36)	1.35 (−0.59 to 3.29)	.170
DASS-S	14.08 ± 9.98	13.64 ± 10.12		
Difference[a] in DASS-S	−1.82 (−3.16 to −0.49)	−2.02 (−3.36 to −0.69)	−0.20 (−2.53 to 2.12)	.865
Week 8 vs week 0	−2.59 (−4.47 to −0.71)	−2.86 (−4.74 to −0.98)	−0.27 (−2.92 to 2.39)	.844
Week 16 vs week 8	−1.06 (−2.98 to 0.86)	−1.19 (−3.11 to 0.73)	−0.14 (−2.85 to 2.58)	.921
DASS-D	8.63 ± 8.32	8.26 ± 8.56		
Difference[a] in DASS-D	−1.58 (−2.78 to −0.38)	−1.85 (−3.06 to −0.65)	−0.28 (−2.41 to 1.86)	.800
Week 8 vs week 0	−2.81 (−4.41 to −1.21)	−2.94 (−4.54 to −1.34)	−0.13 (−2.39 to 2.13)	.910
Week 16 vs week 8	−0.35 (−2.16 to 1.46)	−0.77 (−2.59 to 1.05)	−0.42 (−2.99 to 2.14)	.746

NOTE. Values are mean ± standard deviation or mean (95% CI).
[a]Differences in questionnaires: estimated means for both study periods combined: week 8 vs enrollment and week 16 vs week 8.

supplementation in the treatment of fatigue.[34] In light of the dysregulated Trp metabolism in IBD with a shift toward the kynurenine arm, the direct precursor of serotonin, 5-HTP, was used for the current trial.[14,16] This treatment indeed led to an increase in serum 5-HTP and serotonin levels, whereas kynurenine levels remained unchanged. Nevertheless, the increase in 5-HTP levels did not modulate the IBD-related fatigue.

The lack of understanding of the multifactorial etiology of fatigue hampers the development of adequate treatment strategies. Limited treatment options are currently available, which mainly include psychological interventions.[47,48]

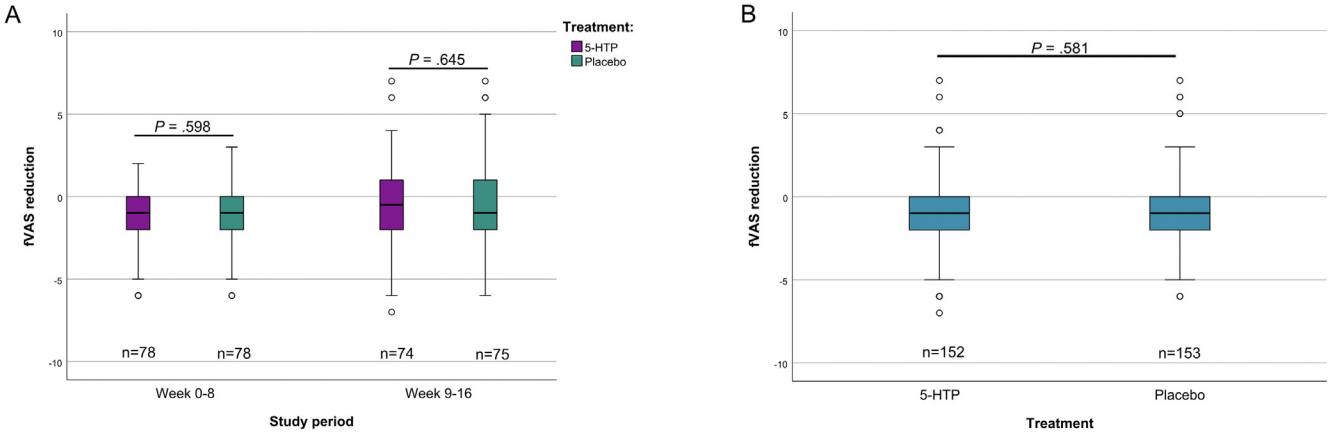

Figure 2. Reduction in fVAS score after 5-HTP treatment. Reduction of fVAS at (*A*) weeks 8 and 16 and (*B*) combined for both study periods. Box-and-whisker plot: The *horizontal line* in the middle of each *box* indicates the median; the *top and bottom borders* of the box mark the 75th and 25th percentiles, respectively, the *whiskers* mark the minimum and the maximum value, and the *circles* indicate outliers.

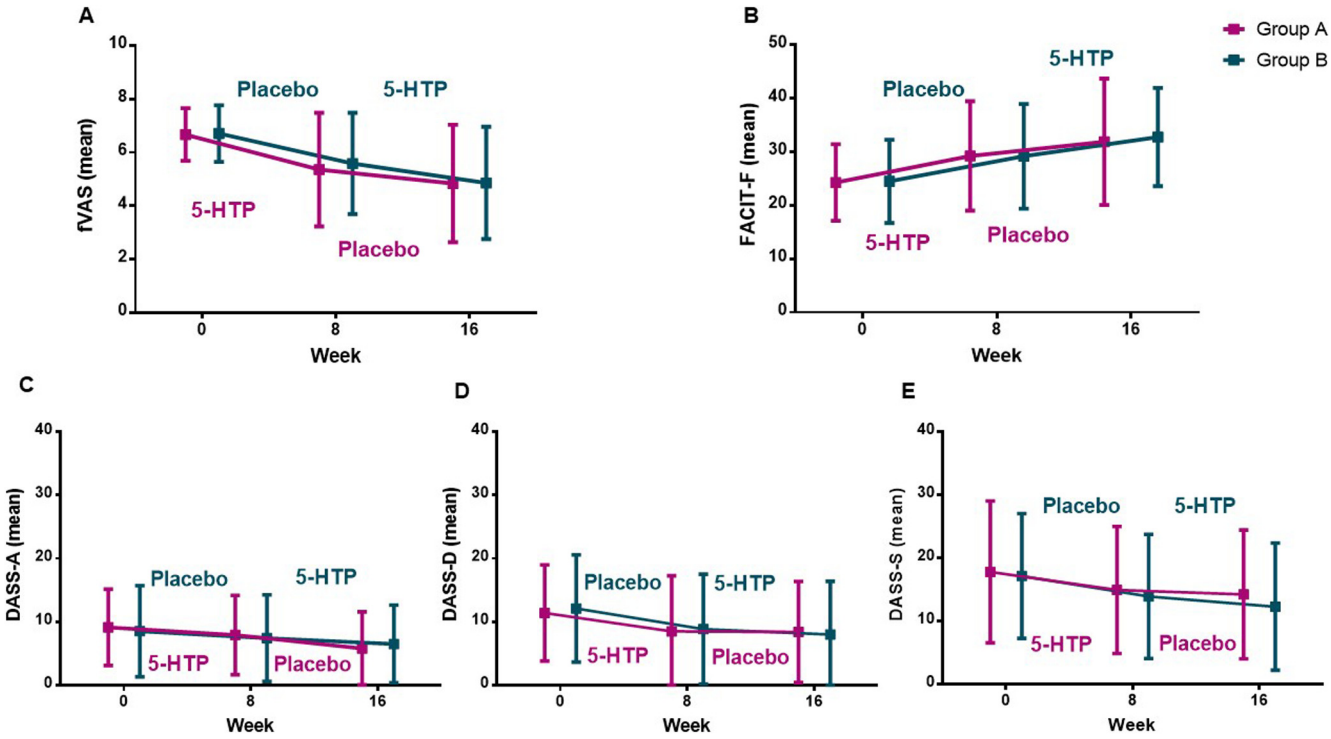

Figure 3. Evolution of the different patient-reported outcomes in both study groups. A comparable decrease in (*A*) fVAS, (*B*) FACIT-F, (*C*) DASS-A, (*D*) DASS-D, and (*E*) DASS-S was seen in both study groups. Group A, 5-HTP then placebo. Group B, placebo then 5-HTP. The mean and standard deviation are plotted.

This is further supported by the current trial that showed a high placebo effect in alleviating fatigue, potentially due to additional clinical support.

Despite the baseline exclusion of patients with depression, up to 45% of patients reported moderate to severe depressive symptoms (DASS-D ≥14) at enrollment, which is higher than the prevalence of 25.2% identified in a recent meta-analysis.[49] Moreover, symptoms of moderate to severe anxiety were found in 43.2% of patients, which also exceeds the prevalence of 32.1% reported in the aforementioned meta-analysis.[49] The same was observed for the baseline stress rate, which was higher compared with a recent

Table 3. Evolution of Tryptophan Metabolites After Treatment

	Treatment		LMM analysis: 5-HTP vs placebo	
Variable	Placebo (n = 144)	5-HTP (n = 147)	Estimated mean difference [95% CI]	*P* value
Kynurenine, *μmol/L*	2.91 (2.47–3.62)	3.01 (2.50–3.62)		
Difference[a] in kynurenine	0.04 [−0.12 to 0.19]	0.08 [−0.08 to 0.24]	0.04 [−0.23 to 0.31]	.752
Week 8 vs week 0	0.03 [−0.18 to 0.23]	0.10 [−0.10 to 0.30]	0.08 [−0.21 to 0.36]	.601
Week 16 vs week 8	0.05 [−0.19 to 0.29]	0.06 [−0.18 to 0.30]	0.01 [−0.33 to 0.34]	.955
5-HTP, *ng/mL*	66.95 (57.10–76.86)	85.45 (66.73–127.29)		
Difference [a] in 5-HTP	−16.36 [−24.16 to −8.56]	36.30 [28.51–44.09]	52.66 [39.34–65.98]	<.001
Week 8 vs week 0	0.25 [−7.52 to 8.02]	36.30 [28.57–44.03]	36.05 [25.09–47.01]	<.001
Week 16 vs week 8	−32.97 [−46.55 to −19.40]	36.30 [22.27–49.87]	69.27 [50.08–88.47]	<.001
Serotonin, *ng/mL*	7.42 (5.27–10.06)	8.76 (6.63–11.88)		
Difference [a] in serotonin	−0.72 [−1.28 to −0.15]	2.28 [1.72–2.85]	3.0 [1.97–4.03]	<.001
Week 8 vs week 0	0.18 [−0.61 to 0.96]	2.56 [1.77–3.34]	2.38 [1.27–3.49]	<.001
Week 16 vs week 8	−1.61 [−2.43 to −0.79]	2.01 [1.19–2.83]	3.62 [2.46–4.78]	<.001

NOTE. Values are median (IQR) or mean [95% CI].
[a]Differences in metabolites: estimated mean for both study periods combined: week 8 vs enrollment and week 16 vs week 8. Missing values for differences in metabolites: placebo, n = 1; 5-HTP, n = 3.

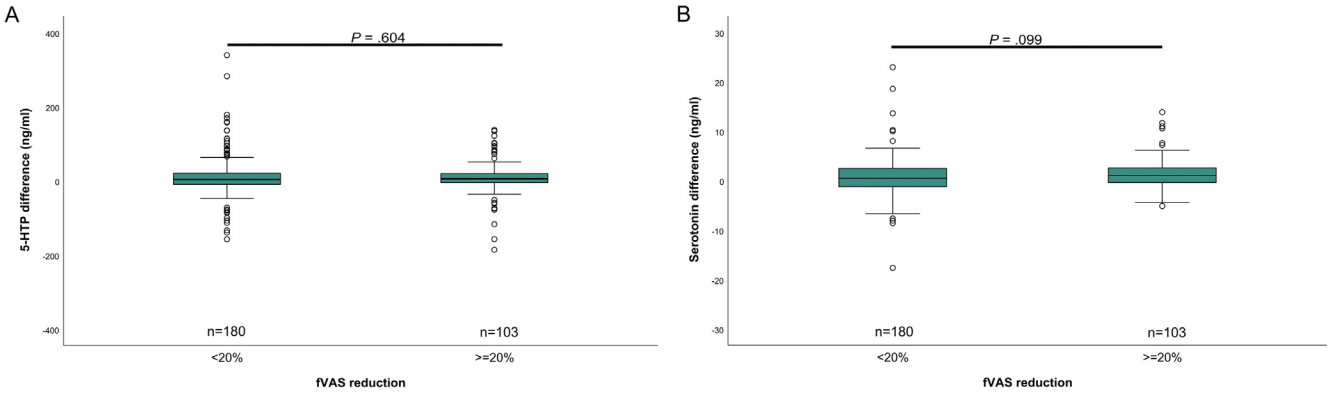

Figure 4. Evolution of serum (*A*) 5-HTP and (*B*) serotonin levels in patients who achieved <20% and ≥20% reduction in fVAS. Box-and-whisker plot: The *horizontal line* in the middle of each *box* indicates the median; the *top and bottom borders* of the box mark the 75th and 25th percentiles, respectively, the *whiskers* mark the minimum and the maximum value, and the *circles* indicate outliers.

survey assessing the prevalence of stress in patients with IBD during the COVID-19 pandemic (29.7%) but lower compared with the 56.6% rate of stress in the studies of Cheema et al[50] and Mules et al.[51] Because the trial specifically included patients with fatigue at baseline, this can explain the higher levels of stress, anxiety, and depression compared with a general IBD population. Nevertheless, this trial further supports the importance of screening for psychological comorbidities in IBD, especially in patients with fatigue.[52] Patients with IBD in remission and with psychological comorbidities have been shown to have a higher chance of future adverse outcomes such as flare-ups and IBD-related hospitalization.[53] Therefore, psychological support and a multidisciplinary approach are warranted in patients with coinciding anxiety or depression.[54]

The current study is a large RCT that assessed the effect of an intervention on fatigue in patients with IBD in clinical and biological remission and emphasizes the very important placebo effect. This study has several other strengths, including the inclusion of a well-defined fatigued population with IBD in remission and the minimal dropout rate in combination with high compliance. Moreover, the multicentered design, incorporating both academic and nonacademic hospitals, ensured a broad representation of the IBD population.

The current study had some limitations. A clear CD preponderance was seen, probably due to the inclusion criterion of treatment with immunomodulators or biologicals, or both, because patients with CD are more frequently treated with biologicals compared with patients with UC.[55] Remission was defined based on clinical and biochemical indices; however, ongoing subclinical inflammation, which can be related to fatigue,[56] was not assessed. Sleep quality was not assessed; thus, it is impossible to relate the fatigue burden to the quality of sleep in this study cohort.

Some factors could have influenced the results of this trial. First, an optimal dose for 5-HTP has not yet been defined, and varying doses were previously tested for the treatment of depression.[35] In the study of Jangid et al[57] a dose of 150 mg was already efficient for depression; however, with increased dosage up to 400 mg and longer duration of treatment, an increase in effectiveness was seen. Therefore, it is possible a greater effectiveness could have been seen with higher doses of 5-HTP or longer duration of treatment, or both. However, in the study of Caruso et al[36] an effect of 5-HTP on fatigue in fibromyalgia patients was already noted after 30 days of treatment, and in the study of Bager et al,[8] thiamine showed effectiveness for IBD-related fatigue after 4 weeks of treatment.

Secondly, a favorable evolution of fatigue scores was seen after both placebo and 5-HTP treatment, likely the consequence of inclusion in a clinical trial. The role of a supportive patient-clinical relationship, such as in a clinical study, has been demonstrated in patients with IBS[58] and in the study of Bruera et al,[59] where a daily telephone call was thought to influence the high placebo effect on cancer-related fatigue.

Finally, the crossover design of this study did not include a washout period, which might have led to a carryover effect biasing the results. Nevertheless, the clear absence of an effect of 5-HTP was already obvious at week 8, before the crossover. Moreover, because 5-HTP has a very short half-life, no carryover effects should be expected 8 weeks later, which was also indicated by the reduction in serum 5-HTP levels after placebo.[60]

Conclusion

Even though treatment with 5-HTP led to a significant increase in serum 5-HTP and serotonin levels, no evidence was found on the efficacy of oral 5-HTP in alleviating fatigue among patients with IBD in remission.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2022.07.052

References

1. Romberg-Camps MJ, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg cohort. Inflamm Bowel Dis 2010;16:2137–2147.
2. D'Silva A, Fox DE, Nasser Y, et al. Prevalence and risk factors for fatigue in adults with inflammatory bowel disease: a systematic review with meta-analysis. Clin Gastroenterol Hepatol 2022;20:995–1009.e7.
3. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. Nat Rev Gastroenterol Hepatol 2019; 16:247–259.
4. Radford SJ, McGing J, Czuber-Dochan W, et al. Systematic review: the impact of inflammatory bowel disease-related fatigue on health-related quality of life. Frontline Gastroenterol 2021;12:11–21.
5. Hindryckx P, Laukens D, D'Amico F, et al. Unmet needs in IBD: the case of fatigue. Clin Rev Allergy Immunol 2018;55:368–378.
6. Geldof J, LeBlanc J-F, Lucaciu L, et al. Are we addressing the top 10 research priorities in IBD? Frontline Gastroenterol 2020;12:564–569.
7. McGing JJ, Radford SJ, Francis ST, et al. Review article: The aetiology of fatigue in inflammatory bowel disease and potential therapeutic management strategies. Aliment Pharmacol Ther 2021;54:368–387.
8. Bager P, Hvas CL, Rud CL, et al. Randomised clinical trial: high-dose oral thiamine versus placebo for chronic fatigue in patients with quiescent inflammatory bowel disease. Aliment Pharmacol Ther 2021;53:79–86.
9. McNelly AS, Nathan I, Monti M, et al. The effect of increasing physical activity and/or omega-3 supplementation on fatigue in inflammatory bowel disease. Gastrointest Nurs 2016;14:39–50.
10. Banovic I, Gilibert D, Jebrane A, et al. Personality and fatigue perception in a sample of IBD outpatients in remission: a preliminary study. J Crohns Colitis 2012; 6:571–577.
11. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. Inflamm Bowel Dis 2006;12:697–707.
12. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. J Crohns Colitis 2017;11:165–174.
13. Lieberman HR, Agarwal S, Fulgoni VL 3rd. Tryptophan intake in the US adult population is not related to liver or kidney function but is associated with depression and sleep outcomes. J Nutr 2016;146:2609s–2615s.
14. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2020;17:223–237.
15. Chen L-M, Bao C-H, Wu Y, et al. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease. J Neuroinflammation 2021;18:1–13.
16. Gupta NK, Thaker AI, Kanuri N, et al. Serum analysis of tryptophan catabolism pathway: correlation with Crohn's disease activity. Inflamm Bowel Dis 2012; 18:1214–1220.
17. Arijs I, Wollants W-J, Clarke G, et al. P096 Analysis of the tryptophan metabolism and indoleamine 2, 3-dioxygenase expression (IDO) in patients with inflammatory bowel disease before and after infliximab treatment. J Crohns Colitis 2014;8:S102–S102.
18. Bosi A, Banfi D, Bistoletti M, et al. Tryptophan metabolites along the microbiota-gut-brain axis: an interkingdom communication system influencing the gut in health and disease. Int J Tryptophan Res 2020;13: 1178646920928984.
19. Nikolaus S, Schulte B, Al-Massad N, et al. Increased tryptophan metabolism is associated with activity of inflammatory bowel diseases. Gastroenterology 2017; 153:1504–1516.e2.
20. Sofia MA, Ciorba MA, Meckel K, et al. Tryptophan metabolism through the kynurenine pathway is associated with endoscopic inflammation in ulcerative colitis. Inflamm Bowel Dis 2018;24:1471–1480.
21. Yamamoto S, Ouchi Y, Onoe H, et al. Reduction of serotonin transporters of patients with chronic fatigue syndrome. Neuroreport 2004;15:2571–2574.
22. Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 2018;23:716–724.
23. Iskandar HN, Linan EE, Patel A, et al. Self-reported sleep disturbance in Crohn's disease is not confirmed by objective sleep measures. Sci Rep 2020;10:1980.
24. Lamas B, Richard ML, Leducq V, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nat Med 2016;22:598–605.
25. Monteleone I, Rizzo A, Sarra M, et al. Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract. Gastroenterology 2011;141:237–248, 248.e1.
26. Rothhammer V, Mascanfroni ID, Bunse L, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat Med 2016;22:586–597.
27. Lieben CK, Blokland A, Westerink B, et al. Acute tryptophan and serotonin depletion using an optimized tryptophan-free protein-carbohydrate mixture in the adult rat. Neurochem Int 2004;44. 9–6.
28. Williams WA, Shoaf SE, Hommer D, et al. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. J Neurochem 1999;72:1641–1647.
29. Pusceddu MM, Barboza M, Keogh CE, et al. Nod-like receptors are critical for gut-brain axis signalling in mice. J Physiol 2019;597:5777–5797.
30. Ogawa S, Fujii T, Koga N, et al. Plasma l-tryptophan concentration in major depressive disorder: new data and meta-analysis. J Clin Psychiatry 2014; 75:e906–e915.

31. Kurz K, Fiegl M, Holzner B, et al. Fatigue in patients with lung cancer is related with accelerated tryptophan breakdown. PloS One 2012;7:e36956.
32. Schroecksnadel K, Fiegl M, Prassl K, et al. Diminished quality of life in patients with cancer correlates with tryptophan degradation. J Cancer Res Clin Oncol 2007; 133:477–4785.
33. Ormstad H, Verkerk R, Amthor KF, et al. Activation of the kynurenine pathway in the acute phase of stroke and its role in fatigue and depression following stroke. J Mol Neurosci 2014;54:181–187.
34. Borren NZ, Plichta D, Joshi AD, et al. Alterations in fecal microbiomes and serum metabolomes of fatigued patients with quiescent inflammatory bowel diseases. Clin Gastroenterol Hepatol 2021;19:519–527.e5.
35. Turner EH, Loftis JM, Blackwell AD. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. Pharmacol Ther 2006;109:325–338.
36. Caruso I, Puttini PS, Cazzola M, et al. Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia syndrome. J Int Med Res 1990; 18:201–209.
37. Puttini PS, Caruso I. Primary fibromyalgia syndrome and 5-hydroxy-l-tryptophan: a 90-day open study. J Int Med Res 1992;20:182–189.
38. Klusmann B, Fleer J, Tovote KA, et al. Trajectories of fatigue in inflammatory bowel disease. Inflamm Bowel Dis 2021;27:1919–1930.
39. Borren NZ, Tan W, Colizzo FP, et al. Longitudinal trajectory of fatigue with initiation of biologic therapy in inflammatory bowel diseases: a prospective cohort study. J Crohns Colitis 2020;14:309–315.
40. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31:1896–1902.
41. Grimstad T, Norheim KB, Isaksen K, et al. Fatigue in newly diagnosed inflammatory bowel disease. J Crohns Colitis 2015;9:725–730.
42. Pollard L, Choy E, Gonzalez J, et al. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology 2006;45:885–889.
43. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541–1544.
44. Keszthelyi D, Troost F, Jonkers D, et al. Visceral hypersensitivity in irritable bowel syndrome: evidence for involvement of serotonin metabolism–a preliminary study. Neurogastroenterol Motil 2015;27:1127–1137.
45. Tinsley A, Macklin EA, Korzenik JR, et al. Validation of the functional assessment of chronic illness therapy-fatigue (FACIT-F) in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2011;34:1328–1336.
46. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33:335–343.
47. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. Gut 2014;63:911–918.
48. Artom M, Czuber-Dochan W, Sturt J, et al. Cognitive-behavioural therapy for the management of inflammatory bowel disease-fatigue: a feasibility randomised controlled trial. Pilot Feasibility Stud 2019;5:145.
49. **Barberio B, Zamani M**, Black CJ, et al. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021; 6:359–370.
50. **Cheema M, Mitrev N**, Hall L, et al. Depression, anxiety and stress among patients with inflammatory bowel disease during the COVID-19 pandemic: Australian national survey. BMJ Open Gastroenterol 2021;8: e000581.
51. Mules TC, Swaminathan A, Hirschfeld E, et al. The impact of disease activity on psychological symptoms and quality of life in patients with inflammatory bowel disease—results from the Stress, Anxiety and Depression with Disease Activity (SADD) Study. Aliment Pharmacol Ther 2022;55:201–211.
52. Keefer L, Ballou SK, Drossman DA, et al. A Rome working team report on brain-gut behavior therapies for disorders of gut–brain interaction. Gastroenterology 2022;162:300–315.
53. Fairbrass KM, Gracie DJ, Ford AC. Longitudinal follow-up study: effect of psychological co-morbidity on the prognosis of inflammatory bowel disease. Aliment Pharmacol Ther 2021;54:441–450.
54. Fairbrass KM, Lovatt J, Barberio B, et al. Bidirectional brain–gut axis effects influence mood and prognosis in IBD: a systematic review and meta-analysis. Gut 2022; 71:1773–1780.
55. Yu H, MacIsaac D, Wong JJ, et al. Market share and costs of biologic therapies for inflammatory bowel disease in the USA. Aliment Pharmacol Ther 2018; 47:364–370.
56. **Vogelaar L, de Haar C**, Aerts BR, et al. Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters. Clin Exp Gastroenterol 2017;10:83–90.
57. Jangid P, Malik P, Singh P, et al. Comparative study of efficacy of l-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode. Asian J Psychiatr 2013;6:29–34.
58. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;336:999–1003.
59. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006; 24:2073–2078.
60. Gijsman HJ, van Gerven JM, de Kam ML, et al. Placebo-controlled comparison of three dose-regimens of 5-hydroxytryptophan challenge test in healthy volunteers. J Clin Psychopharmacol 2002;22:183–189.

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Data Availability
Individual participant data will not be shared publicly for the privacy of study participants. Data can be shared at reasonable request to the corresponding author.

Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

Study Design

In total, 13 Belgian centers participated in patient recruitment: University Hospital Ghent, Ghent; University Hospitals Leuven, Leuven; AZ Imelda Bonheiden, Bonheiden;, Maria Middelares, Ghent; Université libre de Bruxelles (ULB) Erasme, Brussels; AZ Sint Lucas, Ghent; AZ Damiaan, Ostend; Centre Hospitalier Universitaire (CHU) Liège, Liège; Université catholique de Louvain (UCL) Namur, Yvoir; UCL Saint Luc, Brussels; CHU Saint-Pierre, Brussels; AZ Nikolaas, Sint-Niklaas; and University Hospital Brussels, Brussels.

Sample Size Calculation

The required sample size was determined based on the study of Dass et al,[1] using a 20% improvement in fVAS as the primary outcome and criteria obtained from an open-label pilot trial. In this preliminary study, 34 patients were included, all in clinical remission and under treatment with immunosuppressants or biologicals.

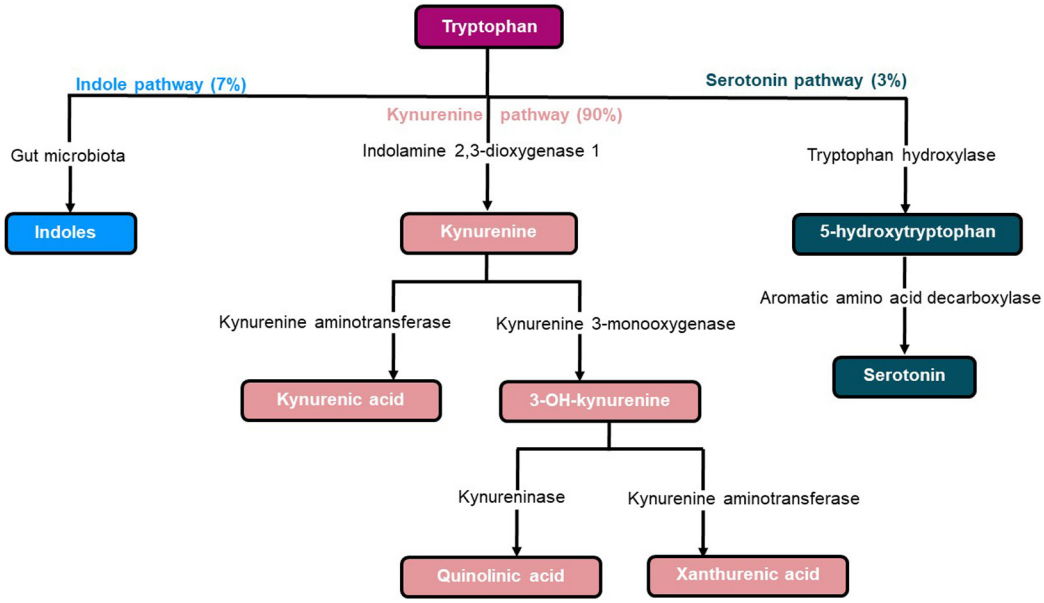
Initially, treatment with 1.5 g of Trp (17 patients) and 3 g of Trp (17 patients) was tested. After 8 weeks of treatment, a significant reduction of fVAS was observed in patients under treatment with 1.5 g/d, but not in patients who received 3 g/d. Globally, a reduction of 20% in fVAS was seen in 40% of the patients, with a dropout of 22%. Interestingly, supplementation with Trp led to an increase in serum serotonin and kynurenine levels.

These data were used for the power analysis, but 5-HTP was selected for the current study because high dosages of Trp are associated with increased conversion of Trp to kynurenine,[2] patients with IBD already have an upregulation of ID01,[3] and increased kynurenine levels could have a potential deleterious effect (as precursors of quinolinic acid). Moreover, 5-HTP has shown increased effectiveness over Trp,[4] and 5-HTP is already commercially available (Levotonine), which were additional arguments to choose 5-HTP over Trp.

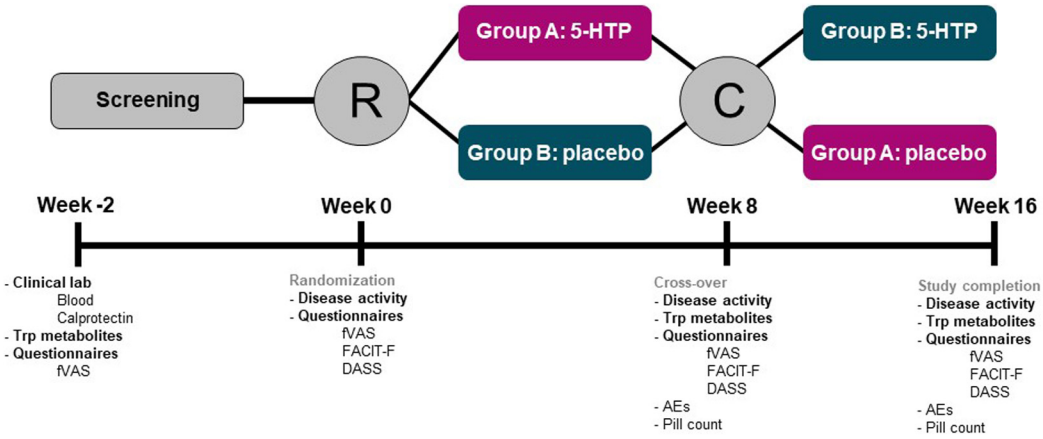
Calculating the sample size for a reduction of $\geq$20% in fVAS (dichotomic response: yes/no), with an expected response in 50% of the treated patients and 30% of the placebo group, assuming a dropout of 22%, the required sample size was 180 patients (90 patients in each treatment arm) for a power of 90% at an α level of 5%.

Supplementary References

1. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541–1544.
2. Birdsall TC. 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Altern Med Rev 1998;3:271–280.
3. Arijs I, Wollants W-J, Clarke G, et al. P096 Analysis of the tryptophan metabolism and indoleamine 2, 3-dioxygenase expression (IDO) in patients with inflammatory bowel disease before and after infliximab treatment. J Crohn Colitis 2014;8:S102–S102.
4. Van Praag H. Studies in the mechanism of action of serotonin precursors in depression. Psychopharmacol Bull 1984;20:599–602.



Supplementary Figure 1. Tryptophan metabolism in physiological conditions.



Supplementary Figure 2. Study flowchart. After successful screening, patients were randomized on a 1:1 basis to group A (5-HTP, followed by placebo) or group B (placebo, followed by 5-HTP). An evaluation was performed at baseline (week 0), after the first (week 8), and after the second (week 16) study period. C, crossover. R, randomization.

Supplementary Table 1. Adverse Events During Treatment

Variable	Placebo (n = 161)	5-HTP (n = 161)	*P* value
Any adverse event	47 (29.2)	56 (34.8)	.282
Potentially 5-HTP related	22 (13.7)	26 (16.1)	.531
Gastrointestinal[a]	6 (3.7)	13 (8.1)	.098
Neurologic/psychological[b]	8 (5)	10 (6.2)	.628
Headache	8 (5)	7 (4.3)	.791
Skin eruptions, myalgia or arthralgia	4 (2.5)	2 (1.2)	.685
Difficulty breathing, rhinitis	2 (1.2)	1 (0.6)	1.000
Sweating	2 (1.2)	1 (0.6)	1.000
Any serious adverse event	1 (0.6)	2 (1.2)	1.000
IBD flare-up[c]	4 (2.5)	2 (1.2)	.685

NOTE. Data are presented as n (%).
[a]Gastrointestinal adverse events: nausea, vomiting, loss of appetite, diarrhea, abdominal pain.
[b]Neurologic/psychological adverse events: loss of concentration, stress/nervousness, irritability, insomnia, dizziness/vertigo, general malaise, possible serotonergic syndrome.
[c]IBD flare-up: physician's global assessment.