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Effects of Cannabidiol Chewing Gum on Perceived Pain and Well-Being of Irritable Bowel Syndrome Patients: A Placebo-Controlled Crossover Exploratory Intervention Study with Symptom-Driven Dosing

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Abstract

Background: Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. Its pathophysiology is diverse and variable, involving disturbed gut–brain interactions, altered motility and secretion, visceral hypersensitivity, increased intestinal permeability, immune activation, and changes in gut microbiota. Complaints experienced by patients suffering from IBS and its co-morbidities strongly impair quality of life (QoL), and available treatments are often unsatisfactory. Anecdotal reports and preclinical data suggest that the endocannabinoid system and functionally related mechanisms could offer treatment targets. Cannabidiol (CBD) is a candidate agent of interest with a broad molecular target profile and the absence of psychoactive properties.

Materials and Methods: In 32 female IBS patients, we explored the effect of a chewing gum formulation containing 50 mg CBD on abdominal pain and perceived well-being in a randomized, double-blinded, placebo-controlled cross-over trial. Chewing gums were used on-demand guided by pain symptoms with a maximum of six per day. Pain intensity was assessed by a visual analogue scale (scale 0.0–10.0), and QoL was evaluated with the IBS-36 questionnaire.

Results: There was no statistically significant difference in pain scores between CBD and placebo at a group level. Subgroup and individual analyses showed a highly variable picture. No indications were found for symptom-driven intake, which also remained lower than expected overall.

Conclusions: With the current design, based on the assumption that IBS patients would adjust their intake to their perceived symptom relief, no differences at the group level were found between CBD and placebo gum in pain scores and the number of gums used. The low use of the gums also indicates that the benefits experienced by these patients generally did not outweigh practical disadvantages such as prolonged chewing throughout the day. The very high intra- and inter-individual variation in IBS symptoms warrant future trials that are more personalized, for example by applying an N-of-1 (rotating) design with individualized dose titration.

Keywords: irritable bowel syndrome; cannabidiol; chewing gum

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain and distension, bloating, and bowel habit abnormalities.[1–3] Its worldwide prevalence is around 10%, with considerable regional differences.[1,2,4] The condition is often accompanied by comorbidities such as fibromyalgia, chronic fatigue syndrome, back and pelvic pain, chronic headache, and temporomandibular joint dysfunction. Symptom patterns, for example bowel habit abnormalities and pain, can vary substantially over time and between individuals. Specific

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diagnostic markers are lacking and IBS is generally diagnosed based on symptoms laid down in the Rome IV diagnostic criteria.[5] Current treatments for IBS include different pharmacological and nutritional strategies, although results are mixed and often disappointing.[2] Regarding its pathophysiology, IBS is mostly considered a disturbed gut–brain interaction characterized by altered gut motility and secretions, changes in microbiota, loss of gut barrier function, visceral hypersensitivity, and immune-mediated processes. However, cause–effect relationships of these manifestations are far from clear.[1–3,6–8] Given its symptomatology and possible mechanisms involved, it is understandable that the endocannabinoid system (ECS) and its associated pathways are considered of interest for IBS treatment.[9,10] It has been known for many years that the ECS plays important roles in intestinal physiology.[11–15] This includes gastric emptying and motility,[16] immunity and inflammation,[15,17] microbiota and barrier function,[18] and gut–brain communication.[19] Ligands of interest are not limited to the endocannabinoids in a strict sense, but they include several other fatty acid conjugates. including palmitoylethanolamine,[15,20–22] oleolylethanolamine,[22] and fatty acid serotonin conjugates.[23] In line with this, relevant receptors not only include CB_1 and CB_2[24–26] but also PPARα and PPARγ,[27–30] TRP channels (TRPV1, TRPV4, TRPA1, TRPM8),[20,31] GPR 55[32,33] and non-receptor targets such as COX-2.[34] In this context, the non-psychoactive compound cannabidiol (CBD) from *Cannabis sativa* has also attracted attention. CBD possesses a broad molecular target profile.[35] Although the compound has very little effect on CB_1 and CB_2 receptors, apart from *in vitro* studies that have suggested that it could antagonize, at low concentrations, their interaction with THC, it is reported to be an agonist at TRPV1 and 5-HT1A receptors, and to enhance adenosine receptor signaling.[36–38] Recently, CBD was found to have inverse agonist activity for GPR3, GPR6, and GPR12 receptors.[39] At low concentrations, CBD blocks GPR55 and TRMP8.[37] At higher concentrations, CBD has been demonstrated to activate PPARγ, TRPV1, and TRPV2.[35,37,38,40] Preclinical studies showed that CBD inhibited inflammatory hypermotility in mice[41] and it displayed anti-inflammatory activity in mouse intestinal segments and in human biopsies.[42]Further, CBD prevented inflammation and inflammation-induced hyperpermeability of the human gut both *in vitro* and *in vivo*.[43,44] A recent review on the effects of CBD on immune responses concludes that CBD has broad immune-suppressive activity in a variety of immune cells.[45] Anecdotal reports suggest that CBD is frequently used by IBS patients, in particular against pain and cramps. However, this is not well documented and clinical studies appear to be lacking in the literature. A reason for this might be the erratic course of the disorder and the large inter-individual differences. A limitation of the effectiveness of CBD, in particular with regards to systemic mechanisms involved in IBS, might be its rapid metabolic conversion after oral administration.[46] Administration via the buccal, sublingual, or oropharyngeal route might improve bioavailability.[47] In addition to a formulation such as drops or a spray, a chewing gum could be used for this. This enabled us to set up the present placebo-controlled trial, in which we explored the usability and effects of a CBD chewing gum on IBS symptoms, focusing on abdominal pain. In view of its likely application in practice, we chose a design in which participants were instructed to use the formulation as needed, and we hypothesized that they would adapt their use to their perceived symptom relief. Our secondary goal was to evaluate the resulting effect on quality of life (QoL).

Materials and Methods

Design

In this 8-week randomized, double-blind, placebo-controlled cross-over trial, the CANdidate Study, the effect of a CBD-containing chewing gum on abdominal pain was compared with a placebo. The study started with a baseline week, followed by two treatment periods of 3 weeks separated by a washout week in between. Patients were randomized to one of the two treatment sequences: group 1 starting with CBD followed by placebo, group 2 starting with placebo followed by CBD. Randomization was done by a random number-generating function in Excel. Participants and researchers remained blinded until all data were analyzed. The protocol was approved by the METC (Medical Ethics Committee) of Wageningen University and Research. The ClinicalTrials.gov identifier of this study was NCT03003260.

Study population

Via patient files of the Gastroenterology Department of the Gelderse Vallei Hospital in The Netherlands, patients were informed that they could register for participation in this study. Both men and women were initially to be included, who had to be diagnosed with IBS according to the Rome III/IV criteria[5] by a

gastroenterologist, were aged between 18 and 65 years of age, and experienced per week at least three moments of pain with a visual analogue scale (VAS) score of 4.0 or higher, measured on a scale of 0.0–10.0. Patients were excluded if they: (i) had a history of intestinal surgery that might interfere with the outcome of the study, (ii) had used cannabis preparations within 3 months before screening, (iii) consumed >7 alcohol units per week, (iv) were hypersensitive to ingredients of the chewing gum, v) used an opioid analgesic or a selective serotonin reuptake inhibitor, and (vi) used a CYP3A4 or CYP2C19 substrate drug. Extra exclusion criteria for female patients of childbearing age were (vii) pregnancy, (viii) breastfeeding, or (ix) no use of a contraceptive pill.

Intervention

Participants were provided with either CBD or placebo chewing gums, just before the start of the intervention periods. A gum contained either 50 mg CBD in food-grade purified hemp seed oil or hemp seed oil only. Manufacturing of the gums was according to GMP guidelines by Axim Biotechnologies. Gums (1.25 g; Ø 15 mm) were spearmint—peppermint flavored and contained gum base, sweeteners, hemp seed oil (with or without CBD) on silicium dioxide support, anti-caking agents, and coloring.

Because our aim was to test whether pain diminished when using the CBD gum, patients were asked to take the chewing gum only when they experienced a pain score of 4.0 or higher on a VAS of 0.0–10.0. They were asked to chew for minimally 30 min per gum, because peak absorption of CBD was within this time frame as determined in a pilot data in four subjects (data not shown). A maximum of six gums per day was set for ethical reasons. If participants would still experience pain at this maximal dose, they were instructed to contact their gastroenterologist. Although a dose of 300 mg per day would still be well below toxic doses,[48] this was considered a signal requiring medical assistance.

Outcomes

Pain intensity was estimated with a VAS device consisting of a stainless steel ruler, with cartoons representing subjective feelings of pain on the front side and a 0.0–10.0 analogue scale on the back. Patients were instructed to note their pain scores, other information on their medical condition, and changes in their defecation pattern in a diary during the whole study period, including the run-in week and wash-out week in which no gum was used. Pain scores at the beginning of a pain period and 30 min later had to be reported with the requirement of a minimal starting pain score of 4.0. The 30-min within-individual change in VAS score was the difference between these two measures. Participants were asked to discriminate between IBS pain and pain moments during menses and acute pain when possible. Adverse events, if occurring, were also noted in the diary. QoL was evaluated with the validated IBS-36 questionnaire, which includes 36 items on the impact of IBS symptoms on QoL, each item scoring on a 0–6 Likert rating scale. A maximum score of 216 stands for a maximal impact.[49] QoL was assessed after weeks 1, 4, 5, and 8.

Statistics

Sample size calculation was based on a published pilot study that used a VAS score for pain after rectal distension.[50] Sample size was calculated with the formula $n = ((Z_\alpha + Z_\beta)^2 \times SD^2)/D^2$ with n as total sample size, D as the difference between treatments, and standard deviation (SD) for the treatment effects To detect a minimal treatment effect of 20% ($D = 2.0$, difference on a VAS of 0.0–10.0), with a power of 80% ($1 - \beta = 0.8416$) and a two-sided significance level of 5% ($\alpha = 1.9600$), assuming an SD of difference in VAS score of 4.0 [SD pilot study = 28 on a VAS of 0–100, so 2.8 on a scale of 0.0–10.0; SD of $\text{difference}_{\text{between 2 measurements}} = \sqrt{(\sum SD^2{}_{\text{of each measurement}})} = \sqrt{(2(SD^2))} = 4$], calculated sample size (n) for this study is 32. Taking into account a dropout rate of 25%, the initial number of subjects to be included was 40.

Data from the run-in period were used for the baseline characteristics of the total study population and the two treatment order (=sequence of intervention) groups. Characteristics were expressed as means with SD or medians with interquartile range. Effect on pain was estimated as the effect on within-individual change in VAS score between the beginning and end of a 30-min, IBS-related pain period. The VAS starting score of such a 30-min pain period was required to be minimal (4.0). The treatment effect was defined as the within-individual difference in effect on pain after use of CBD minus the effect after placebo. Data from the wash-out period were not used. Effect on QoL was estimated as the within-individual difference between QoL score at the end of the CBD and placebo intervention period. The individual treatment effects of VAS and QoL scores were assessed for normality by the Kolmogorov–Smirnov test and by visual inspection of box plots and histograms of the data points. These

within-individual differences in outcomes were tested by the paired-samples *T*-test if normally distributed. In case of non-normality, the non-parametric Wilcoxon signed rank test was used. For differences between the two independent treatment order groups, we used the unpaired-samples *T*-test or the non-parametric Mann–Whitney *U*-test, depending on distribution of the VAS and QoL scores. The assumption of no carryover effect was tested by comparing the treatment effect of the two independent treatment order groups. The assumption of no periodical effect was tested by comparing all the within-individual differences in within-individual change in VAS scores of the two intervention periods and all the within-individual differences in QoL at the end of weeks 4 and 8. Again, depending on distribution of these differences, the paired-samples *T*-test or the Wilcoxon signed rank test was used. In case no data were reported in one of the treatment periods, the participant was excluded from analysis. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. For data analysis, we used the statistical software package SPSS, version 23.0.

Results

Initially, 411 patients of the Gastroenterology Department of the Gelderse Vallei Hospital were evaluated for potential eligibility by staff members of the University department of Human Nutrition. In- or exclusion was based on data in patient files. The 266 patients who met the criteria received a general announcement and were asked to apply. Forty people agreed to participate and they were randomized to the treatment groups. Five patients did not complete the study, of whom two reported unpleasant air ingestion due to chewing the gums. Apart from this adverse event, the gums were tolerated well. Another three patients were excluded because of missing data. Finally, 32 participants were included for statistical analysis of the VAS data. For analysis of the QoL data, two extra patients were excluded because of missing data. The study flow scheme is illustrated in Figure 1.

The 32 participants completing the trial were all women, with a median age of 31 years. Between the two treatment order groups there was a difference in baseline change in pain intensity during a 30-min pain period (Table 1), which was non-significant (Mann–Whitney *U* test $p = 0.08$). During the treatment periods, less than one gum per day was used: The mean number of CBD gums used during the three intervention weeks was 18.2 (range 1–71), and the mean number of placebo gums during 3 weeks was 17.0 (range 1–60). The mean number of gums used in the total study population was 5.9 per week; sequence group 1, starting with CBD, used 5.4 gums per week; sequence group 2 used 6.3 gums per week. This difference was not statistically significant (Mann–Whitney *U* test $p = 0.20$). In the total study population, the mean number of gums used in the second intervention period was higher than in the first period (6.5 and 5.3, respectively), but the difference was not statistically significant (Wilcoxon signed rank test $p = 0.35$). Use of chewing gum reduced pain (Fig. 2), but there was no statistically significant difference in treatment effect between CBD and placebo. The mean within-individual difference in 30-min reduction in pain score after CBD compared with placebo was 0.1, 95% CI [−0.3 to 0.5], $p = 0.61$ (Table 2). Subgroup analysis suggested a minor treatment effect in the sequence group starting with placebo (mean within-individual difference in pain reduction of 0.4, 95% CI [−0.2 to 1.0]), but this was not significant, $p = 0.16$. Of the 17 participants starting with the placebo gum, 6 experienced a treatment effect larger than 1.0 (1.1 to 2.7), compared with an effect of 1.6 in one participant in the group starting with CBD. However, there was no statistically significant difference in treatment effect between the two sequence groups (Mann–Whitney *U* test $p = 0.12$). In the total study population, there was a non-significant difference in treatment effect between the two intervention periods: The mean 30-min change in VAS score in the second intervention period was 0.3 higher, 95% CI [0.0 to 0.7] ($p = 0.08$). Finally, with respect to treatment effect on QoL, there was no significant effect of CBD compared with placebo; mean difference in QoL score was −1.0, 95% CI [−6.8 to 4.9] ($p = 0.74$) (Table 3). However, QoL of the total study population was higher in the first intervention period, and mean difference was 7.0, 95% CI [2.0 to 12.4] ($p = 0.01$).

Discussion

Given the expected use of the chewing gum in practice, we had deliberately opted for administration on demand and we hypothesized that participants would adapt their use to their perceived symptom relief. However, a first practical limitation that emerged was that several participants reported that 30 min periods of chewing during the day were difficult to combine with their daily activities. Several patients took considerably lower numbers of chewing gums than we had

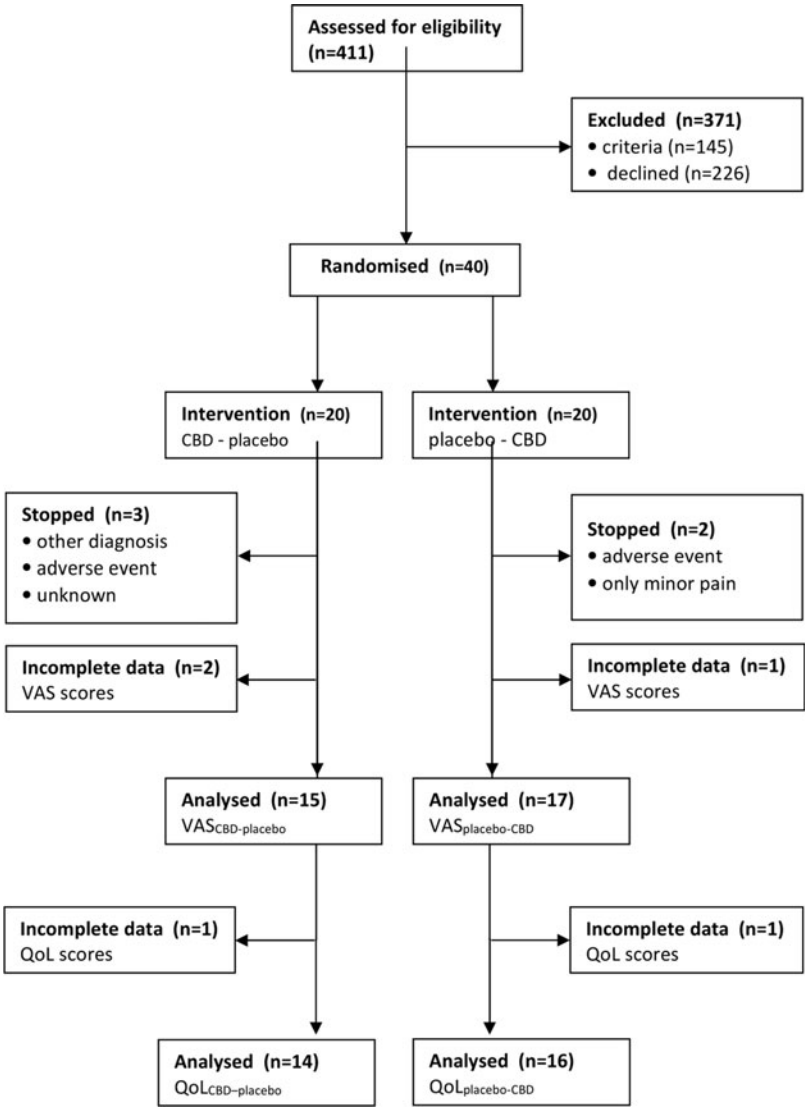

FIG. 1. Flow diagram of the CANdidate study.

predicted from their pre-study evaluation questionnaires. At the same time, we presume that pronounced positive effects during pain episodes would have been noted by our participants and resulted in higher use. At a group level, we did not find an effect of the CBD chewing gum compared with placebo on IBS-related abdominal pain intensity or on perceived well-being. QoL was also unaffected. A second and even more important limitation of our study was the considerable within-person and between-person variations observed, which might have masked potential effects in specific forms of IBS. However, analysis of pain scores from individual patients did not point toward such effects. One of the requirements for inclusion was the occurrence of minimal 3 pain periods per week with 4.0 as minimal VAS score; 4 of the original 40 patients had to be excluded after enrolment because their pain was below this threshold or data were incomplete. Another requirement for inclusion was the occurrence of minimal three pain periods per week with 4.0 as minimal VAS score. This led to the dropout of another four patients. Variation in symptoms and intensity also inherently contributed to measurement inaccuracies. The VAS pain score measured with a ruler combined with a numeric rating scale (NRS) is a sensible measure of abdominal pain intensity. The

Table 1. Characteristics of a Population of 32 Female Outpatients with Irritable Bowel Syndrome, Expressed as Total Number, Mean (Standard Deviation), or Median [interquartile range]

Characteristic	Total population	Sequence group 1, CBD—placebo	Sequence group 2, placebo—CBD
Subjects, *N*	32	15	17
Age, years	31 [22–50]	38 [23–52]	29 [22–45]
QoL	103 (29)	99 (28)	108 (31)
Pain periods, *N*[a]	10.5 [5.0–14.0]	8.0 [5.0–14.0]	12.0 [4.0–14.0]
VAS start 30 min[b]	5.8 (1.0)	5.9 (0.8)	5.7 (1.1)
VAS end 30 min[c]	4.9 (1.3)	5.4 (0.9)	4.6 (1.5)
VAS change[d]	0.9 (0.2)	0.6 (0.8)	1.2 (0.9)

Measured during baseline week.
[a]Median total number of 30 min pain periods (starting VAS score ≥4.0).
[b]Mean individual VAS score at start of 30 min pain periods.
[c]Mean individual VAS score at end of 30 min pain periods.
[d]Mean within-individual change in VAS score between start and 30 min later of an IBS-related pain period; VAS starting score of a pain period should be minimal (4.0).

CBD, cannabidiol; IBS, irritable bowel syndrome; QoL, quality of life score (QoL is assessed with the IBS-36 questionnaire, including 36 items on the impact of IBS symptoms on QoL; maximum score is 216); VAS, visual analogue scale (for subjective rating of pain intensity on a scale of 0–10).

NRS is classified as a valid method to measure clinically relevant response.[51] However, this patient-reported outcome is subjective and quantifies only one dimension of pain, its severity. The IBS-36 questionnaire is a validated measure of QoL; it is easy to perform and specifically designed for IBS patients, which takes also other aspects of pain into account as well as other IBS symptoms.[49] Ten participants used fewer than three gums per week during both intervention periods, resulting in fewer measurements of change in pain. Additional factors that contributed to the unexpected low usage of gums included exclusion of pain moments during menses and poor dental condition. In the absence of comparable studies, the dose of 50 mg per chewing gum and a maximum dose of 300 mg were based on literature data,[52] clinical reports, and ongoing clinical studies as posted on the clintrial.gov database. In general, a wide range of oral doses are reported for CBD in the literature, with most between 100 and 800 mg/day. As we did not perform dose titrations in our study, it could be that the dose used may have been too low. We found slightly different results depending on treatment order. An explanation might be that in the baseline week the mean 30-min change in pain score differed between the groups. This baseline difference might have differentially influenced treatment effects. We had very limited data available on the absorption characteristics of the chewing gum formulation used. A small pilot study performed in our lab before the study with four volunteers using a lower dose (10 mg [$n=2$] and 30 mg [$n=2$]) resulted in CBD plasma peak levels occurring between 1 and 2 h after taking the formulation. Internal studies by the manufacturer with the 50 mg dose showed peak

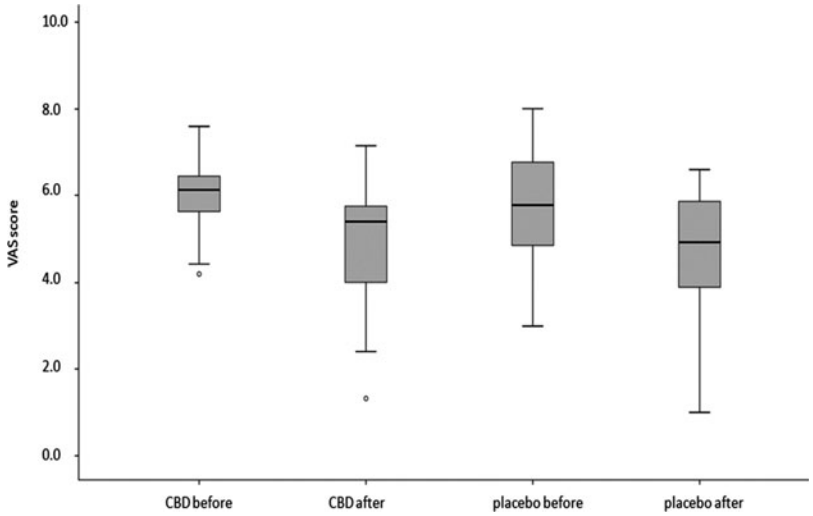

FIG. 2. VAS scores just before and 30 min after the start of chewing a CBD or placebo gum, in a population of 32 female outpatients with IBS. Threshold for gum use was abdominal pain with a VAS score of minimal 4.0. CBD, cannabidiol; IBS, irritable bowel syndrome; VAS, visual analogue scale.

Table 2. Within-Individual Change in Visual Analogue Scale-Score During 30-Min Pain Periods Directly After Intervention, in a Population of 32 Female Outpatients with Irritable Bowel Syndrome

Intervention groups	Intervention period Week 2–4	Intervention period Week 6–8	Within-individual comparison intervention CBD—placebo[a]
Sequence group 1	CBD	placebo	CBD—placebo
Subjects, *N*	15	15	15
Gums,[b] *N* [IQR]	10 [6–26]	9 [4–24]	
VAS change (SD), [95% CI]	0.5 (0.7)	0.8 (0.9)	−0.3 (1.0) [−0.8 to 0.3]
Sequence group 2	Placebo	CBD	CBD—placebo
Subjects, *N*	17	17	17
Gums, *N* [IQR]	18 [9–22]	14 [8–34]	
VAS change (SD), [95% CI]	1.4 (1.3)	1.8 (1.5)	0.4 (1.1) [−0.2 to 1.0]
Both groups 1 and 2			CBD—placebo
Subjects, *N*			32
Gums, *N* [IQR]			26 [13–55]
VAS change (SD), [95% CI]			0.1 (1.1), [−0.3 to 0.5]
T-test for paired samples			$p = 0.61$

[a]Within-individual difference in within-individual change in VAS score between start and 30 min later of an IBS-related pain period, after intervention with CBD compared with placebo; VAS starting score of a pain period should be minimal (4.0).
[b]Median number of gums used during intervention.
CI, confidence interval; IQR, interquartile range; SD, standard deviation.

levels at ~1.5 h. These observations are in agreement with what has been reported for oro-mucosal administration using sprays or drops.[47] The substantial between-person variation in number of gums used makes it impossible to speculate on effective dosing.

Table 3. Quality of Life Scores in a Population of 32 Female Outpatients with Irritable Bowel Syndrome

Intervention groups	Intervention period Week 2–4	Intervention period Week 6–8	Within-individual comparison intervention CBD—placebo[a]
Sequence group 1	CBD	Placebo	CBD—placebo
Subjects, *N*	14	14	14
Gums, *N* [IQR]	11 [6–26]	9 [5–27]	
QoL (SD), [95% CI]	102.8 (33.3)	98.3 (39.8)	6.7 (14.3), [−1.6 to 15.0]
Sequence group 2	placebo	CBD	CBD—placebo
Subjects, *N*	16	16	16
Gums, *N* [IQR]	18 [9–22]	15 [9–36]	
QoL (SD), [95% CI]	102.9 (34.6)	95.3 (28.9)	−7.6 (14.0), [−15.1 to −0.2]
Both groups 1 and 2			CBD—placebo
Subjects, *N*			30
Gums, *N* [IQR]			26 [16–55]
QoL (SD), [95% CI]			−1.0 (15.7), [−6.8 to 4.9]
T-test, paired samples			$p = 0.74$

[a]Within-individual difference in QoL score after intervention with CBD compared with placebo.

Compliance was tested by checking the diaries and counting the residual gums of each participant. Considering the disorder and the formulations used, placebo effects are likely to play a considerable role. It is known that chewing stimulates the cephalic-vagal reflex, which directly affects gut motility and gut hormone secretion.[53] External validity was further restricted by the fact that none of the male participants—already underrepresented after enrolment—were included in the final analyses.

To conclude, to our knowledge this is the first, be it small, published placebo-controlled clinical study that evaluated the effect of CBD on IBS symptoms. Although no significant effects at group level were found, this preliminary trial adds to our knowledge about the potential application of CBD in IBS, and it provides directions for the design of potential further studies. Demonstrating either efficacy or inefficacy of a compound in IBS patients presents a considerable challenge. Considering that economical reasons make trials with CBD involving hundreds of IBS patients highly unrealistic, our results underline the need for more sophisticated and individualized designs in the future. To this end, the methodology of a series of double-blinded, randomized, placebo-controlled trials in single patients, N-of-1 trials,[54] combined with individualized dose-titration and monitoring CBD plasma concentrations seems an attractive option.

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Author Disclosure Statement

No competing financial interests exist.

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A.C.B.v.O., N.M.d.R., and R.F.W. are employed by Wageningen University (the Netherlands). B.J.M.W is a gastroenterologist at the Hospital Gelderse Vallei (Ede, The Netherlands) and professor at Wageningen University. S.M. was involved as an MSc student during the study and is currently a PhD student at the Amsterdam Medical Centre. R.F.W. has been a member of de Axim Biotechnologies scientific advisory board until 2018, for which he received no financial

compensation. Axim provided the study materials (chewing gums) in 2017, and financially supported the logistic and administrative costs connected with the study. Axim had no influence in the design and performance of the study and writing of the article. All rights and patents on the study products were transferred in July 2020 from Axim to APIRx Pharmaceuticals B.V.

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Abbreviations Used

CBD = cannabidiol
CI = confidence interval
ECS = endocannabinoid system
IBS = irritable bowel syndrome
IQR = interquartile range
NRS = numeric rating scale
QoL = quality of life
SD = standard deviation
VAS = visual analogue scale