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Randomised clinical trial: the efficacy of gut-directed hypnotherapy is similar to that of the low FODMAP diet for the treatment of irritable bowel syndrome

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SUMMARY

Background
A low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet is effective in treating irritable bowel syndrome (IBS).

Aim
To compare the effects of gut-directed hypnotherapy to the low FODMAP diet on gastrointestinal symptoms and psychological indices, and assess additive effects.

Methods
Irritable bowel syndrome patients were randomised (computer-generated list), to receive hypnotherapy, diet or a combination. Primary end-point: change in overall gastrointestinal symptoms across the three groups from baseline to week 6. Secondary end-points: changes in psychological indices, and the durability of effects over 6 months.

Results
Of 74 participants, 25 received hypnotherapy, 24 diet and 25 combination. There were no demographic differences at baseline across groups. Improvements in overall symptoms were observed from baseline to week 6 for hypnotherapy [mean difference (95% CI): −33 (−41 to −25)], diet [−30 (−42 to −19)] and combination [−36 (−45 to −27)] with no difference across groups ($P = 0.67$). This represented ≥20 mm improvement on visual analogue scale in 72%, 71% and 72%, respectively. This improvement relative to baseline symptoms was maintained 6 months post-treatment in 74%, 82% and 54%. Individual gastrointestinal symptoms similarly improved. Hypnotherapy resulted in superior improvements on psychological indices with mean change from baseline to 6 months in State Trait Personality Inventory trait anxiety of −4(95% CI −6 to −2) $P < 0.0001$; −1(−3 to 0.3) P = ns; and 0.3(−2 to 2) P = ns, and in trait depression of −3(−5 to −0.7) $P = 0.011$; −0.8(−2 to 0.2) P = ns; and 0.6(−2 to 3) P = ns, respectively. Groups improved similarly for QOL (all $p \leq 0.001$).

Conclusions
Durable effects of gut-directed hypnotherapy are similar to those of the low FODMAP diet for relief of gastrointestinal symptoms. Hypnotherapy has superior efficacy to the diet on psychological indices. No additive effects were observed.

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, affecting approximately 5–12% of the population in Western countries.[1] As there is no known cure for IBS, treatment often requires a multimodal approach where dietary, psychological and pharmacological approaches are common. Dietary therapies are appealing to many IBS sufferers with the most recent strategy to have considerable impact being the restriction of indigestible and slowly-absorbed short-chain carbohydrates, collectively known as FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols).

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols have been shown to induce gastrointestinal symptoms in IBS patients[2] mainly due to their poor and slow intestinal absorption with subsequent osmotically driven increase in small intestinal water content and colonic fermentation producing gas.[3–5] The evidence-base for efficacy of the low FODMAP diet is strong, comprising randomised controlled trials in addition to comparative and observational studies.[6–10] A recent well-powered blinded placebo-controlled cross-over study confirmed previous observations that approximately 70% of IBS patients (regardless of IBS subtype) gain clinically significant benefit when following a diet low in FODMAPs.[11] Furthermore, a comprehensive systematic review and meta-analysis of data from multiple studies has recently supported such efficacy.[12] As such, the low FODMAP diet is increasingly applied by health professionals in patients with IBS as a first-line dietary therapy.[11]

Another promising approach in reducing symptoms in patients with IBS is gut-directed hypnotherapy wherein suggestions for the control and normalisation of gastrointestinal function are made to the subconscious mind.[13] Several controlled trials and observational studies have reported reductions in overall and individual gastrointestinal symptoms in between 24% and 73% of participants with gut-directed hypnotherapy.[14–18] Its potential mechanisms of action on the brain–gut axis are multiple, with evidence spanning psychological effects through to physiological gastrointestinal modifications. Regardless, obtaining similarly robust evidence of efficacy for gut-directed hypnotherapy to that of the low FODMAP diet is constrained by difficulties in designing a blinded placebo.

Participants in psychological studies typically know what intervention they are receiving.[19] Therefore, measuring the effectiveness of a therapy to a no-treatment control condition is inadequate. An alternative is to compare the therapy with an active control group with proven efficacy. The aims of the current study were, therefore, to perform a randomised clinical trial in patients with IBS, but naïve to dietary or psychological therapies, to compare the effect of gut-directed hypnotherapy with the low FODMAP diet, alone or in combination, on abdominal symptoms and psychological health over the short term (6 weeks) and longer term (6 months). It was hypothesised that participants would report similar gastrointestinal and psychological improvements regardless of whether they received gut-directed hypnotherapy or the low FODMAP diet but that those who received both therapies would experience an enhanced effect.

MATERIALS AND METHODS

Participants

Participants were recruited through newspaper advertisements in metropolitan Melbourne, on social media and through the Monash University Department of Gastroenterology webpage. Participants were included if they were ≥18 years of age, met Rome III criteria for IBS and had coeliac disease excluded by either a normal duodenal biopsy on an adequate gluten-containing diet or a negative test for HLA-DQ2 and HLA-DQ8. Exclusion criteria included Marsh I or II lesions on duodenal biopsy, other clinically significant gastrointestinal disease, previously diagnosed or reported psychiatric disorder, excessive alcohol intake, pregnancy or the inability to give written informed consent. Those who had undergone gut-directed hypnotherapy, had been instructed on the low FODMAP diet prior the current study or were coincidently excluding more than one FODMAP category were also excluded.

Study design

Participants were randomised, according to a computer-generated list, to receive gut-directed hypnotherapy (6 weekly 1-h hypnosis sessions for 6 weeks), education on a low FODMAP diet (education at the beginning of week 1, review at week 6) or a combination of both. Long-term gastrointestinal symptom, psychological symptom and dietary adherence data was also collected 6 months post treatment. The study was not blinded. Detailed descriptions of study interventions are described below.

Protocol

All patients were assessed by a Gastroenterologist (HP, PRG) with regard to inclusion and exclusion criteria and the subtype of IBS regarding bowel habit was determined. The effectiveness of the treatments was evaluated using questionnaires that assessed gastrointestinal symptoms and psychological indices concerning anxiety and depression and quality of life (as detailed below). All participants completed the questionnaires prior to treatment and directly after treatment (week 6). Long-term follow-up data were also collected 6 months after completion of the treatment. Follow-up data included gastrointestinal symptoms, psychological symptoms and dietary adherence (for those in the low FODMAP diet and combined treatments) via a usual weekly intake recall questionnaire that was posted to participants with a pre-paid envelope for easy return. Participants were asked to refrain from using any alternative treatment until they had reached the 6-month follow-up timepoint. All participants gave written, informed consent. The protocol was approved by The Alfred Research and Ethics Unit and was registered with the Australian Clinical Trials Registry (ACTRN12612000585820). All authors had access to study data and approved the final manuscript.

Interventions

Gut-directed hypnotherapy. Those randomised to receive gut-directed hypnotherapy underwent 1-h hypnosis sessions weekly for 6 weeks. The sessions were based on the well-established Manchester model.[14] The sessions were scripted (i.e. the same for each participant) and were conducted with an appropriately trained and experienced clinical hypnotherapist (SLP). Participants were provided with a pre-recorded compact disc that was identical to the first session's script and were asked to listen to it daily during the 6-week intervention period. After the gut-directed hypnotherapy intervention was completed, the participants kept the compact disc and were able to listen to it at their choosing. Continued use of the compact disc in the follow-up period was not a requirement of the study. Adherence to gut-directed hypnotherapy was measured according to the attendance at scheduled sessions and to daily use of the compact disc during the intervention phase. Adherence was arbitrarily defined as attending all sessions and no more than two missed days of listening to the compact disc per week over the 6-week study period, as recorded by SLP at each hypnosis session.

Low FODMAP diet. An experienced gastrointestinal dietitian educated the participants in a 1-h session on the principles of the low FODMAP diet including the mechanistic action of FODMAPs at the beginning of week 1. Participants were asked to restrict foods containing high and moderate amounts of all types of FODMAPs and to consume only foods that contained no or low amounts of FODMAPs. They were given written information outlining the principles of the diet, lists of high, moderate and low FODMAP containing foods, instructions on how to read food labels for FODMAPs and several recipe ideas. Participants were instructed to follow the diet strictly from the beginning of week 1 to the end of week 6. Weekly telephone contact was made to encourage compliance. Participants were not permitted to discuss additional matters during this contact. At week 6, participants underwent a review as per current best practice. Those who reported symptomatic improvement at review were educated on the reintroduction phase (detailed below) and those who failed to show improvement were instructed to return previously excluded foods back into the diet (i.e. return to usual diet without following the reintroduction phase). Adherence to the low FODMAP diet was assessed during the weekly telephone contact where direct questioning was used to determine the level of adherence. Adherence was arbitrarily defined as no more than three accidental exposures to high FODMAP containing foods over the 6-week study period.

The reintroduction phase: This phase aimed to liberalise the diet while maintaining good symptomatic control as per current best practice. Tolerance levels for each participant for each FODMAP were determined by reintroducing one FODMAP subgroup per week (except for oligosaccharides) and then monitoring any symptomatic response. Reintroduction of oligosaccharides occurred more gradually where one fructan-containing food (wheat or garlic) was introduced per week. If symptoms were experienced participants stopped the reintroduction and waited until they were symptom-free before reducing the serving size to half and trying again. Alternatively, participants could assume that the FODMAP was a problem for them and continue onto the next FODMAP reintroduction. If symptoms were not experienced, participants could either gradually increase the number of foods that contained the particular FODMAP they were challenging and continue to assess their response (i.e. determining their tolerance threshold) until the amount they previously consumed was reached or

maintain that amount and type of FODMAP in their diet and continue onto the next FODMAP subgroup for reintroduction. This process was continued until each FODMAP subgroup was tested. Since individual participants differed with regard to tolerance levels to each FODMAP, the time taken to undergo the reintroduction phase varied. Information on each participant's FODMAP reintroduction phase was collected at the 6-month follow-up.

Combined treatment. Those in the combined condition received both the gut-directed hypnotherapy and the low FODMAP diet treatments, the first session being held on the same day, in varying order, according to practitioner availability. The remainder of the treatment followed the protocol as described above for each therapy.

Measurements

Gastrointestinal symptoms. Gastrointestinal symptoms were assessed using a 100-mm visual analogue scale, where 0 indicated no symptoms and 100 represented the worst symptoms ever experienced, as previously applied.[2, 11] The visual analogue scale score was used to measure overall gastrointestinal symptoms, abdominal pain, bloating, wind, satisfaction with stool consistency and nausea. The gastrointestinal visual analogue scale is part of the validated IBS Symptom Severity Scale questionnaire.[20] Individual differences of 20 mm or more over time were arbitrarily considered clinically significant, as previously applied.[9]

Psychological indices. Anxiety and depression were assessed using the State Trait Personality Inventory (STPI),[21] and the Hospital Anxiety and Depression Scale (HADS).[22] The STPI was selected based on simplicity, validity and reliability.[21] It is an 80-item self-report questionnaire, with eight 10-item subscales for measuring state and trait anxiety, depression, curiosity and anger. However, only anxiety and depression subscales were calculated for the current study. State items were used to assess current emotional state and were measured on a 4-point intensity scale, where 1 = not at all; and 4 = very much so. Trait items assessed emotional disposition and were rated on a 4-point intensity scale, where 1 = almost never; and 4 = almost always. The range of possible scores for each subscale can vary from a minimum of 10 to a maximum of 40. The HADS is widely accepted with good reliability and validity for the assessment of anxiety and depressive symptoms.[23] It consists of 14 items, with seven items relating to anxiety and seven to depression. A 4-point Likert scale was used, with higher scores indicating greater symptoms.

Quality of life. The IBS quality of life was used to determine disease specific health-related quality of life.[24] The instrument includes 34 items that are measured on a 5-point Likert scale, where 1 = not at all; and 5 = a great deal. To facilitate the interpretation of scores, the summed total score is transformed to a 0–100 scale, with 100 representing the best possible quality of life score.

Long-term follow-up

Long-term follow-up data were collected 6 months post treatment. Gastrointestinal symptoms and psychological indices concerning anxiety, depression and quality of life were assessed as outlined above. Information on whether any alternative treatments had subsequently been undertaken was also obtained. In addition, participants in the low FODMAP diet and combined treatments completed a checkbox questionnaire that identified their current dietary status in terms of whether they continued to follow the low FODMAP diet strictly or following reintroduction of foods as instructed (referred to as 'attenuated' low FODMAP diet) or had stopped following the diet altogether. Data on the long-term use of the compact disc was not obtained from those undergoing gut-directed hypnotherapy.

End-points

The primary end-point was the change in overall gastrointestinal symptoms across the gut-directed hypnotherapy, low FODMAP diet and combined treatment groups from baseline to week 6 as measured by the visual analogue scale. Secondary end-points included the change in overall gastrointestinal symptoms across the three groups from baseline to 6 months post treatment; the change in individual symptoms of abdominal pain, bloating, wind, satisfaction with stool consistency and nausea across the three groups from baseline to week 6 and 6 months post treatment; the change in psychological indices concerning anxiety, depression and in quality of life across the gut-directed hypnotherapy, low FODMAP diet, and combined treatment groups from baseline to week 6 and 6 months post treatment as measured by the STPI, HADS and IBS quality of life.

Statistical analysis

Power calculations were based on previous data[16] and allowed for drop-out, missing data and error rate. Using the change in overall gastrointestinal symptoms from

baseline to the end of the intervention (week 6) as the primary end-point, 78 participants were required to detect a statistically significant difference between groups given an effect size of 0.2 with 80% power at a two-sided 5% significance level. Intention-to-treat analyses were performed on all data from baseline to week 6 but per-protocol analyses were applied for data from baseline to 6 months as there was no satisfactory way of dealing with the participants who failed to return their long-term follow-up questionnaires. Participants who were enrolled and randomised, but, who withdrew prior to any intervention were excluded from the analysis. Symptom data of participants who started treatment (during week 1) but withdrew prior to the end of week 6 were included and adjusted by carrying forward the last observation. Mixed between-within subjects analysis of variance (ANOVA) was conducted to assess the impact of treatment condition (gut-directed hypnotherapy, the low FODMAP diet and the combined condition) across time for overall gastrointestinal symptoms. One-way between groups ANOVA and *t*-tests were used to assess the change from baseline for each outcome measure. The relationship between overall gastrointestinal symptoms and psychological indices for each treatment was determined using Pearson product-moment correlation coefficient. The regression coefficient (r^2) estimates the amount of variation in all measured psychological indices that can be attributed to changes in overall gastrointestinal symptoms. Type 1 error was controlled by use of the False Discovery Rate adjustment technique. Statistical analyses were performed using IBM SPSS statistics version 21 (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism Version 6.01 (GraphPad Software, San Diego, CA, USA).

RESULTS

Patients

Of 146 individuals who responded to advertisements, 78 fulfilled the inclusion criteria and were enrolled into the study. Four participants withdrew prior to the initiation of the randomised intervention. One participant became injured and could not fulfil attendance requirements, one travelled overseas due to unforeseen circumstances, one revealed a previous diagnosis of diverticular disease and one failed to attend the first treatment session. Two further participants started treatment but withdrew prior to week 6 (during weeks 3 and 5; both in the combined treatment). No differences in demographic features (Table 1), gastrointestinal symptoms or psychological indices (Table 2) were identified at baseline between treatment groups. Sixty-two participants (84%) completed and returned the 6-month follow-up questionnaire.

Adherence during the interventions

Adherence to the low FODMAP diet was achieved in 21 participants (88%) in the low FODMAP diet and 19 (76%) in the combined treatment group with no difference observed between groups. Non-adherence was largely the result of >3 accidental exposures to high FODMAP foods but no participant abandoned the diet completely. Adherence to daily listening of the compact disc in the gut-directed hypnotherapy treatment group was achieved in 18 participants (72%) and 19 participants (80%) in the combined treatment group. Only three participants reported to ceasing listening to the compact disc completely.

Effect on gastrointestinal symptoms (Table 3, Figures 1 and 2)

The two-way ANOVAS revealed significant improvements in overall gastrointestinal symptoms from baseline for treatment groups at both the 6 week ($F(1,71) = 150.92$, $P < .001$, $\eta^2 = 0.68$) and 6-month time points ($F(1,71) = 81.53$, $P < .001$, $\eta^2 = 0.54$), but no significant differences across treatment groups (6 weeks: $F(2,71) = 0.48$, $P = 0.62$, $\eta^2 = 0.01$; 6 months: $F(2,71) = 1.17$, $P = 0.32$, $\eta^2 = 0.03$) and no significant

Table 1 | Participant demographics at baseline between treatment groups

	Gut-directed hypnotherapy	Low FODMAP diet	Combined treatment	*P* value
No. of participants	25	24	25	ns
Gender, male, %	3 (21)	5 (36)	6 (43)	ns
Median age (range), years	40 (20–72)	34 (23–66)	39 (23–63)	ns
IBS subtype (%)				
Diarrhoea	7 (28)	10 (42)	13 (52)	ns
Constipation	11 (44)	5 (21)	7 (28)	
Mixed/alternating	7 (28)	9 (37)	5 (20)	

Table 2 | Participant gastrointestinal, psychological and quality of life characteristics at baseline between treatment groups. Data shown represents the mean (95% CI)

	GDH	LFD	Combined	*P*-value
Gastrointestinal symptoms				
Overall	65 (60–70)	61 (54–68)	62 (56–69)	NS
Pain	53 (44–63)	53 (44–63)	54 (44–64)	NS
Bloating	68 (61–75)	59 (50–67)	58 (47–70)	NS
Wind	69 (60–77)	63 (55–71)	61 (52–70)	NS
Stool consistency	62 (51–73)	70 (60–81)	58 (46–69)	NS
Nausea	25 (14–37)	22 (13–32)	24 (10–37)	NS
Psychological measures				
STPI State anxiety	17 (15–19)	18 (16–20)	18 (15–20)	NS
STPI State depression	19 (17–21)	19 (17–21)	19 (17–21)	NS
SPI Trait anxiety	21 (19–23)	21 (19–23)	21 (18–23)	NS
STPI Trait depression	18 (16–21)	17 (15–19)	19 (16–22)	NS
HADS anxiety	8 (6–10)	8 (7–10)	9 (7–11)	NS
HADS depression	4 (3–5)	3 (2–4)	4 (3–6)	NS
IBS-QOL	56 (46–65)	57 (47–68)	60 (53–67)	NS

Table 3 | Change in overall and individual gastrointestinal symptoms from baseline to week 6 and 6 months post treatment. Comparisons made by paired-samples *t*-tests. Data shown represents the mean difference (95% CI)

	Baseline to week 6						Baseline to 6 months					
	GDH	*P* value	LFD	*P* value	Combined	*P* value	GDH	*P* value	LFD	*P* value	Combined	*P* value
Overall	−33 (−41 to −25)	<0.0001	−30 (−42 to −19)	<0.0001	−36 (−45 to −27)	<0.0001	−38 (−50 to −27)	<0.0001	−30 (−43 to −16)	<0.0001	−27 (−40 to −14)	<0.0001
Pain	−27 (−37 to −16)	<0.0001	−26 (−39 to −14)	<0.0001	−31 (−42 to −20)	<0.0001	−33 (−46 to −20)	<0.0001	−30 (−41 to −20)	<0.0001	−29 (−41 to −16)	<0.0001
Bloating	−35 (−46 to −24)	<0.0001	−37 (−51 to −24)	<0.0001	−36 (−48 to −24)	<0.0001	−40 (−53 to −28)	<0.0001	−29 (−41 to −17)	<0.0001	−30 (−45 to −15)	<0.0001
Wind	−37 (−50 to −25)	<0.0001	−41 (−53 to −30)	<0.0001	−34 (−43 to −24)	<0.0001	−32 (−43 to −19)	<0.0001	−33 (−46 to −20)	<0.0001	−29 (−43 to −15)	<0.0001
Stool consistency	−33 (−43 to −23)	<0.0001	−42 (−54 to −29)	<0.0001	−32 (−45 to −19)	<0.0001	−35 (−47 to −22)	<0.0001	−34 (−47 to −21)	<0.0001	−23 (−38 to −8)	0.009
Nausea	−14 (−22 to −5)	0.003	−11 (−20 to −1)	0.03	−16 (−27 to −5)	0.008	−17 (−28 to −6)	0.005	−10 (−23 to 4)	ns	−12 (−26 to 1)	ns

interaction between time and treatment group (6 weeks: $F(2,71) = 0.32$, $P = 0.73$, $\eta^2 = 0.01$; 6 months: $F(2,71) = 1.79$, $P = 0.17$, $\eta^2 = 0.03$) were identified. This pattern of outcomes reflects an equivalent change from baseline for each treatment group but no difference between treatment groups at both the 6 week and 6-month time intervals. The outcomes from a further two-way ANOVA of the overall gastrointestinal symptom data between 6 weeks and 6 months suggest no main effect of time ($F(1,71) = 1.53$, $p = .22$, $\eta^2 = 0.02$) or treatment groups ($F(2,71) = 0.22$, $P = 0.81$, $\eta^2 = 0.006$) but a significant interaction between time and treatment group ($F(2,71) = 4.41$, $P = .016$, $\eta^2 = 0.11$). This interaction was driven by an increase in overall gastrointestinal symptoms between 6 weeks and 6 months for the combined treatment group ($P = 0.004$) but no change was observed for either the gut-directed hypnotherapy or the low FODMAP diet groups ($P = 0.37$ and $P = 0.99$ respectively) over the same time period. No differences in individual symptoms of abdominal pain, bloating, wind and stool consistency were observed across groups from baseline to week 6 and 6 months post treatment. All individual symptoms improved in each treatment group. Improvement in nausea was observed across all treatment groups at week 6, but only those who received gut-directed hypnotherapy maintained improvement at 6-months.

Eighteen of the 25 participants receiving gut-directed hypnotherapy (72%), 17/24 of those receiving the low FODMAP diet (71%) and 18/25 (72%) receiving the combined treatment, improved at week 6. This improvement relative to baseline symptoms was maintained at 6 months post treatment in 74% receiving gut-directed hypnotherapy, 82% the low FODMAP diet and 54% of

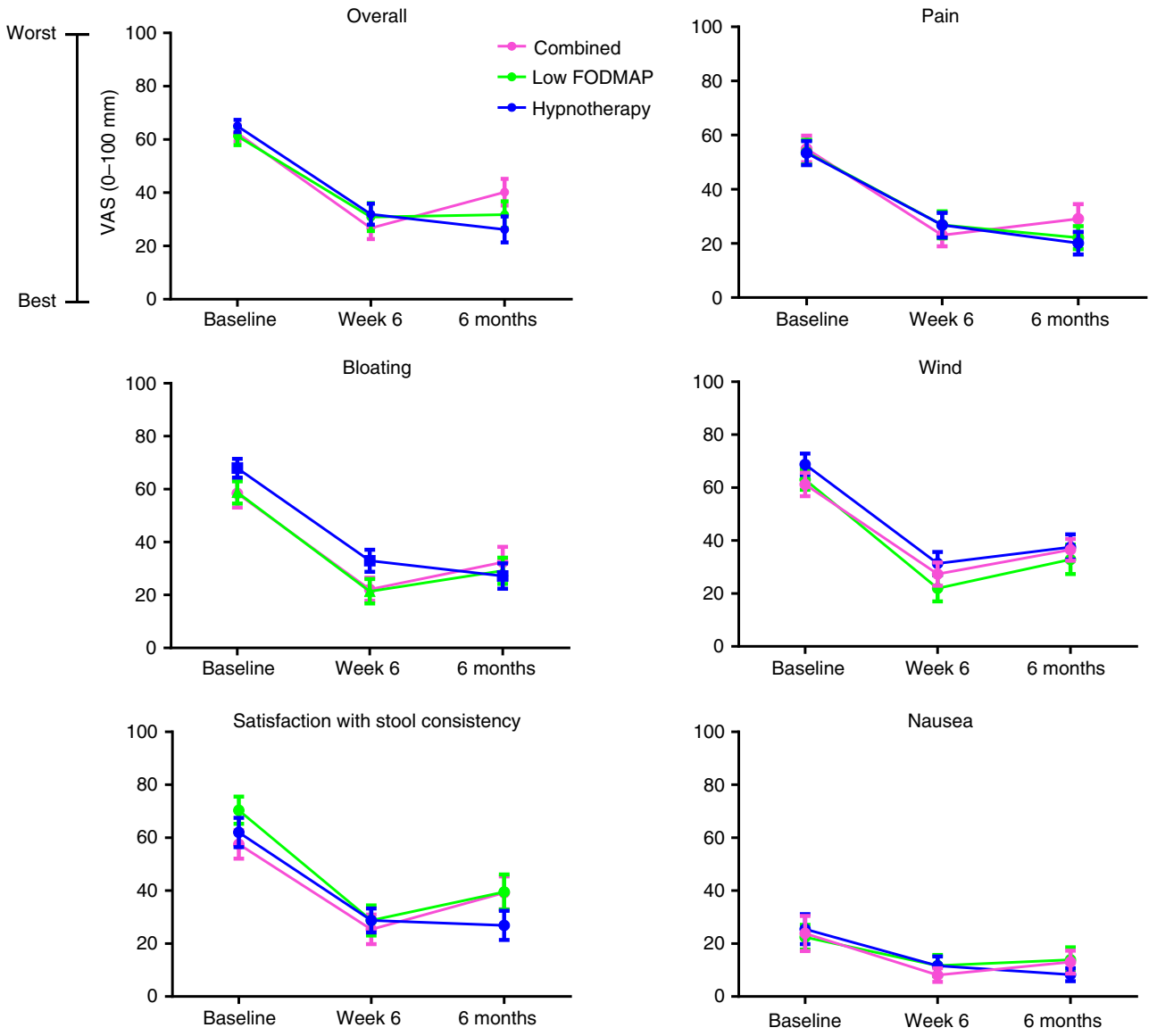

Figure 1 | Overall and individual gastrointestinal symptom improvement over time and between treatment groups. Data were analysed using a mixed between-within subjects ANOVA. There were no significant differences in overall or individual gastrointestinal symptoms between treatment conditions at each of the individual time points. Data shown represent the mean ± SEM.

participants receiving the combined treatment. Worsening of symptoms, as defined as an increase of ≥20 mm on the visual analogue scale from baseline to 6 months post treatment, was reported in one participant in the gut-directed hypnotherapy group (4%), four in the low FODMAP diet group (18%) and seven (32%) in the combined group (Figure 2).

Effect on psychological status (Table 4, Figure 3)

No significant change in state anxiety or depression was observed across or within the gut-directed hypnotherapy, low FODMAP diet or combined treatment from baseline to week 6 or 6 months post treatment (Table 4). No change in trait anxiety or depression was observed at either time-point for those in the low FODMAP diet or combined treatments. However, as illustrated in Figure 3, trait anxiety and depression significantly reduced in participants who received gut-directed hypnotherapy from baseline to 6 months post treatment.

As shown in Table 4 and Figure 3, HADS anxiety was significantly reduced in all three treatment groups from baseline to week 6 but was only maintained 6 months

post treatment for those in the gut-directed hypnotherapy and low FODMAP diet treatments. No difference in the degree of improvement at week 6 was observed across treatment groups ($p = 0.90$; one-way repeated-measures ANOVA). HADS depression significantly improved from baseline to week 6 in those who received the low FODMAP diet or combined treatments, but this was not maintained at 6 months post treatment. Only a trend for a reduction in HADS depression was observed from baseline to week 6 for those patients who received gut-directed hypnotherapy, but this was the only treatment to reach statistical significance 6 months post treatment.

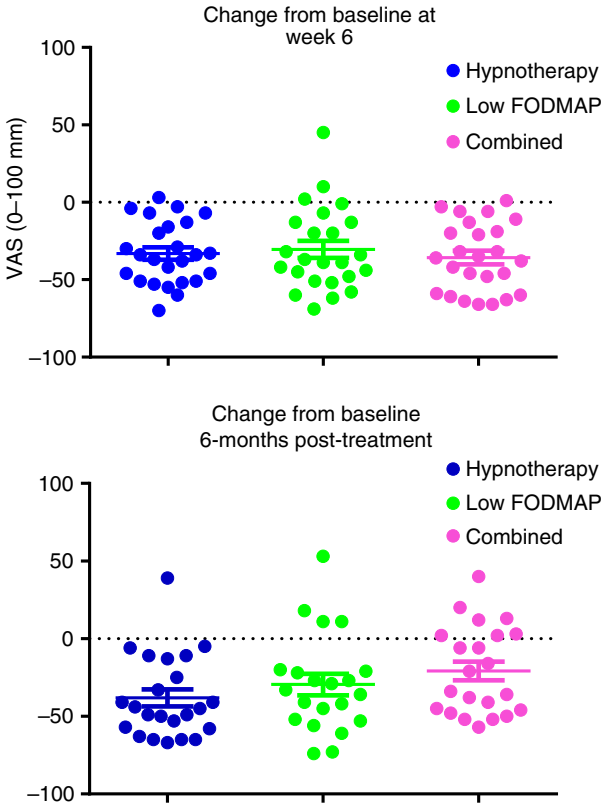

Figure 2 | Change in overall gastrointestinal symptoms from baseline to week 6 and 6 months post treatment. No difference in improvement was seen between treatment groups. Data shown represent mean ± SEM.

Effect on quality of life (Table 4 and Figure 3)

Irritable bowel syndrome quality of life was significantly improved in all three treatment groups by a mean of 14–20 points (all $P < .0001$) from baseline to week 6, and by 12–21 points from baseline to 6 months post treatment. There was no difference in the change across the groups.

Correlations

In order to determine whether changes in overall gastrointestinal symptoms were associated with changes in psychological indices for each treatment at the 6-week and 6-month time points, Pearson product-moment correlation coefficients were calculated. No correlations between overall gastrointestinal symptoms and psychological indices concerning anxiety, depression or quality of life were identified for any treatment group from baseline to week 6. From baseline to 6 months post treatment, overall gastrointestinal symptoms were directly associated with state depression ($r = 0.49$; $r^2 = 0.24$), trait anxiety ($r = 0.42$; $r^2 = 0.18$) and HADS

Table 4 | Change in psychological status and quality of life from baseline to week 6 and 6 months post treatment. Comparisons made by paired-samples *t*-tests. Data shown represents the mean difference (95% CI)

	Baseline to week 6						Baseline to 6 months					
	GDH	*P* value	LFD	*P* value	Combined	*P* value	GDH	*P* value	LFD	*P* value	Combined	*P* value
STPI state												
Anxiety	−0.0 4 (−3 to 2)	ns	−2 (−5 to −0.1)	ns	−2 (−4 to 0.6)	ns	−2 (−4 to 0.7)	ns	−1 (−4 to 2)	ns	0.5 (−3 to 4)	ns
Depression	−0.6 (−2 to 1)	ns	−1 (−3 to 1)	ns	−1 (−2 to 0.1)	ns	−2 (−4 to −0.1)	ns	−1 (−3 to 1)	ns	0.2 (−2 to 2)	ns
STPI trait												
Anxiety	−2 (−3 to −0.3)	ns	−2 (−3 to −0.2)	ns	−0.4 (−2 to 1)	ns	−4 (−6 to −2)	<0.0001	−1 (−3 to 0.3)	ns	0.3 (−2 to 2)	ns
Depression	−1 (−2 to −0.01)	ns	−0.9 (−2 to 0.4)	ns	−1 (−3 to 0.5)	ns	−3 (−5 to −0.7)	0.011	−0.8 (−2 to 0.2)	ns	0.6 (−2 to 3)	ns
HADS												
Anxiety	−2 (−3 to −0.2)	0.023	−2 (−3 to −0.6)	0.003	−2 (−3 to −1)	<0.0001	−3 (−4 to −1)	0.001	−2 (−4 to −0.1)	0.037	−1 (−3 to 0.2)	ns
Depression	−0.8 (−2 to 0.0 5)	ns	−1 (−2 to −0.1)	0.032	−1 (−2 to −0.0 6)	0.038	−2 (−3 to −1)	0.001	−1 (−2 to 0.3)	ns	−0.4 (−2 to 0.7)	ns
IBS-QOL	20 (14–26)	<0.0001	14 (7–20)	<0.0001	14 (9–19)	<0.0001	20 (13–28)	<0.0001	21 (12–30)	<0.0001	12 (5–19)	0.001

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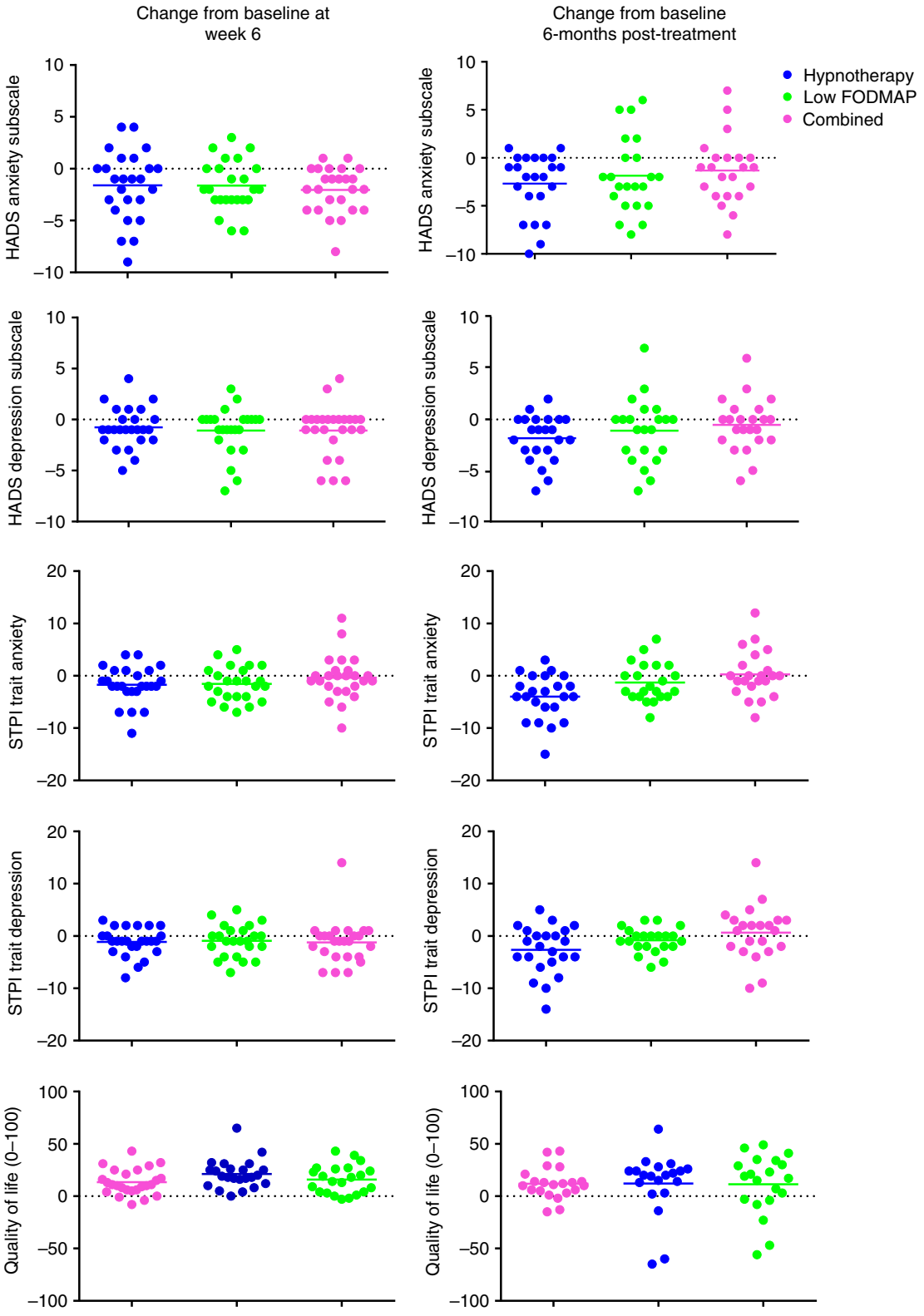

Figure 3 | Change in HADS anxiety and depression and STPI anxiety and depression and quality of life from baseline to week 6 and 6 months post treatment. Data shown represent the mean. *$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$.

anxiety ($r = 0.72$; $r^2 = 0.52$) and depression scores ($r = 0.49$; $r^2 = 0.24$; all $P < 0.05$) in the low FODMAP diet group. Overall gastrointestinal symptoms were directly associated with state ($r = 0.46$; $r^2 = 0.21$) and HADS anxiety ($r = 0.54$; $r^2 = 0.29$) in the gut-directed hypnotherapy group and with trait ($r = 0.46$; $r^2 = 0.21$) and HADS depression ($r = 0.47$; $r^2 = 0.22$; all $P < 0.05$) in the combined treatment. No correlations were identified between overall gastrointestinal symptoms and quality of life following any treatment.

Long-term follow-up

Three-month follow-up data are not presented since the presence of a similar improvement relative to baseline was observed at the 6-month time-point. Sixty-two of 74 participants (84%) completed and returned the 6-month follow-up questionnaire. All but two of the participants in the dietary groups (both in the low FODMAP diet only group) achieved an attenuated low FODMAP diet, that is, reintroduced high FODMAP foods into their diet, as instructed by the dietitian. Eleven participants (15%) reportedly broke protocol and tried an alternative treatment/s in the 6 months following study completion, but no difference in adherence was observed between treatment groups ($P = 0.73$). Common alternative treatments included acupuncture, Chinese medicine and dietary changes such as eating a 'healthier diet'. No participants in the gut-directed hypnotherapy treatment group reported trialling the low FODMAP diet or vice-versa.

DISCUSSION

The therapeutic approach in patients with IBS includes dietary, psychological and pharmacological strategies. Obtaining high-quality evidence for efficacy of psychological therapies can be challenging due to the difficulties in designing appropriate placebo interventions. For gut-directed hypnotherapy, large observational cohorts including a recent audit of 1000 adult patients,[25] and small randomised control trials with suboptimal placebo arms have suggested global reductions of gastrointestinal symptoms in the majority of IBS patients.[14–18] An alternative approach is to compare efficacy against that of an intervention with a high level of evidence. The low FODMAP diet benefits all symptoms in a proportion of patients with IBS patients regardless of bowel habit subtype[11] and the recent meta-analysis of multiple studies, including re-evaluation of raw data, indicated that a high level of evidence for its efficacy has been published.[12] Additional randomised controlled trials indicating the efficacy of the low FODMAP diet compared with diets higher in FODMAPs have since been published.[26, 27] Hence, gut-directed hypnotherapy was compared to the low FODMAP diet in patient's naïve to both therapies on the effects on gastrointestinal symptoms (primary end-point), psychological indices concerning anxiety and depression, and quality of life. Since the approaches are thought to be quite different in mechanisms of action, it was anticipated that they would have additive effects. The results of the current randomised control trial clearly show that both therapies are efficacious to a similar degree and have durable benefits, but no sign of an additive effect was evident. With the exception of an improvement in anxiety at 6 months in the low FODMAP diet-treated arm, gut-directed hypnotherapy appeared to have a superior effect of positively modulating psychological indices in the longer term.

The comparator therapy, the low FODMAP diet, showed efficacy in a similar proportion of patients (about 70%) as similarly reported in previous observational and randomised studies.[6–8, 11] The durability of this response previously reported in a prospective observational cohort has been confirmed.[10] However, the actual dietary behaviour of patients taught the low FODMAP diet by a dietitian has not been previously reported. Few patients remained on the strict FODMAP restriction that was recommended as initial therapy. This was likely to be attributable to the reintroduction programme directed by the dietitian so that the patients could liberalise their diets yet still continue to have symptomatic benefits. The interpretation of these data, however, is limited given the disparity in the reintroduction phase between participants who may have individual FODMAP tolerance thresholds.

Gut-directed hypnotherapy achieved almost identical rates of response and mean magnitude of improvement at the end of therapy and at the 6-month follow-up to that of the low FODMAP diet for gastrointestinal symptoms. Likewise, quality of life improved similarly. Despite the very different portals of entry of the interventions (central nervous system vs. luminal), the combination of gut-directed hypnotherapy and the low FODMAP diet achieved response rates similar to either therapy alone and had numerically (although not statistically significantly) worse outcome after 6 months. Several reasons might be entertained for this. First, it might reflect that efficacy associated with the three study arms were placebo effects. Since there was no placebo, this cannot be discounted and must be seriously considered especially

in this patient group and in the absence of objective end-points. It might be argued that the durability of improvement is not a feature observed in pharmacological studies, where drugs are discontinued, whereas the diet and the potential use of the compact disc continue for the ensuing 6 months making such a comparison hazardous. As for most comparative studies, it comes down to the strength of the data in support of the 'gold standard'. While the majority of existing studies support the efficacy of the low FODMAP diet when compared with placebo, the strength of this data has not been uniformly accepted.[28] Secondly, when considering visual analogue scale scores, the detection of an enhanced benefit of combing the two therapies may have been hindered by a ceiling effect. For example, healthy populations have reported similar gastrointestinal symptom scores to those reported at week 6 in all three treatment groups in the current study.[11] Thirdly, despite the different portals of entry, the same disordered physiological processes may be the targets. Perhaps targeting the same pathophysiology resulted in reduced rather than greater symptomatic improvement. Fourthly, the two therapies may have adversely affected each other. Patients may have not adhered to the diet or practised with the compact disc at home as seriously or as well because they felt they were getting a 'double dose'. However, this seems unlikely since no evidence of this was detected in the assessment of adherence to dietary therapy. Finally, the results might reflect the nature of the patients. Up to one-third of patients might not be readily amenable to any therapy and be regarded as have 'recalcitrant' IBS. Conversely, those readily amenable to modulation may respond to either effective therapeutic approach.

Current understanding of the precise mechanism by which gut-directed hypnotherapy exerts an efficacious effect is limited. Regardless, there is strong evidence that gut-directed hypnotherapy can influence both psychological and physiological outcomes including motility, visceral sensitivity, immune function and central processing, as recently reviewed.[13] In the current study, only psychological aspects were addressed. Gut-directed hypnotherapy, but not the low FODMAP diet or the combined treatment, was associated with durable and increasing effect on anxiety and depression when two independent measures were used. Such effects were not apparent early, but emerged at the 6-month assessment. However, symptomatic benefit did not correlate with improvement in psychological indices suggesting that this might not be the predominant mechanism of action for gut-directed hypnotherapy. More work is needed to further elucidate the independent role of gut-directed hypnotherapy in relation to other factors involved in the treatment response.

The effect of restricting FODMAPs on psychological status is of interest, particularly in association with reports of improved depression in women with fructose malabsorption following restriction of fructose intake.[29, 30] When the patients were strictly low FODMAP there were some improvements in psychological status, but such changes correlated with symptomatic improvement, suggesting a causal relationship. However, these improvements were not sustained. If FODMAP intake is indeed associated with anxiety or depression, it would not be anticipated that improvements would be sustained since strict adherence to the low FODMAP diet was not an aim of the study or a feature of the participant's dietary behaviour. The divergence of psychological effects of the low FODMAP diet and gut-directed hypnotherapy does suggest that gut-directed hypnotherapy has specific psychological benefits, not just improvements associated with lower severity of gastrointestinal symptoms.

If expertise to deliver the low FODMAP diet and gut-directed hypnotherapy were available to manage a patient with IBS, it is uncertain which should be applied first. Certainly, the use of combined therapy is not supported. Predictors of response were not identified and the study was not adequately powered to do this effectively. Gut-directed hypnotherapy carries some advantages. Adverse side effects of hypnotherapy are rare and when performed by a qualified and experienced practitioner, gut-directed hypnotherapy is considered exceptionally safe. It is highly effective regardless of patients' individual hypnotic capacities.[25] Disadvantages of gut-directed hypnotherapy include a lack of hypnotherapists skilled in gut-directed techniques, the financial burden of a therapeutic course and the time commitment needed (e.g., six 1-h sessions as performed in the present study).

The low FODMAP diet has the advantage that it utilises the interest in food-choice for better health thereby empowering the patients to influence their condition. However, several potential shortcomings of the low FODMAP diet are worth considering. The first relates to nutritional adequacy, which has only been investigated in one study, where deficient calcium intake was noted.[6] Fibre intake is also at risk since wheat products, legumes and fruit and vegetables are an important part of fibre intake. Secondly, diet appears to be critical in influencing the composition of the microbiome where short-term alternations in dietary fibre intake have been shown to

impact intestinal health.[31] More specifically, recent studies of the effect of altering FODMAP intake on the faecal microbiota have suggested a potential issue with regard to the loss of prebiotic effect of FODMAPs (particularly oligosaccharides) when adherence to the low FODMAP diet is strict,[32] although, in the present study, ongoing strict adherence was discouraged by the instructing dietitians, as per present best practice, and was indeed followed by only a minority of the participants. Furthermore, short-term alterations in dietary fibre intake as a consequence of habitual diet are likely to impact on the microbiome. The third relates to the risk of precipitating an eating disorder such as orthorexia nervosa (the unhealthy obsession with eating healthy food).[33] While not recognised in the current Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the increasing fixation of righteous eating within the community is undeniable. As such, a nondietary therapy, such as gut-directed hypnotherapy, might be useful in preventing the escalation of such growing obsession.

In conclusion, the efficacy for relief of gastrointestinal symptoms and improving quality of life of gut-directed hypnotherapy is similar to that of the low FODMAP diet in IBS patients, within the limitations of the number of patients studied. These modalities do not show evidence of additive effects when concurrently delivered. In contrast to the low FODMAP diet, gut-directed hypnotherapy provides an additional sustained benefit of improved psychological indices concerning anxiety and depression. Given the importance of psychological health in patients with IBS, these data in total might be considered to show that gut-directed hypnotherapy is a superior alternative to the low FODMAP diet. Gut-directed hypnotherapy should be regarded as a viable modality as primary therapy for patients with IBS.

AUTHORSHIP

Guarantor of the article: PRG.

Author contributions: SLP, JGM and PRG were involved in study concept and design; SLP and HP were involved in recruitment, enrolment and assessment of participants; SLP and CKY acquired the data; SLP, GWY and PRG were involved in the analysis and interpretation of data; GWY, JGM and PRG were involved in study supervision; SLP and PRG were involved in drafting of the manuscript; All authors have approved the final draft of the manuscript.

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REFERENCES

1. Hillilä M, Färkkilä M. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. *Aliment Pharm Ther* 2004; **20**: 339–45.
2. Shepherd S, Parker F, Muir J, Gibson P. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008; **6**: 765–71.
3. Ong D, Mitchell S, Barrett J, *et al.* Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol* 2010; **25**: 1366–73.
4. Barrett J, Gearry R, Muir J, *et al.* Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. *Aliment Pharmacol Ther* 2010; **31**: 874–82.
5. Marciani L, Cox E, Hoad C, *et al.* Postprandial changes in small bowel water content in healthy subjects and patients with irritable bowel syndrome. *Gastroenterology* 2010; **138**: 469–77.
6. Staudacher HM, Lomer MC, Anderson JL, *et al.* Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr* 2012; **142**: 1510–8.
7. Staudacher H, Whelan K, Irving P, Lomer M. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet* 2011; **24**: 487–95.
8. De Roest R, Dobbs B, Chapman B, *et al.* The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract* 2013; **67**: 895–903.
9. Biesiekierski J, Peters S, Newnham E, Rosella O, Muir J, Gibson P. No effects of gluten in patients with self-reported non-celiac gluten sensitivity following dietary reduction of low-fermentable, poorly-absorbed, short-chain carbohydrates. *Gastroenterology* 2013; **145**: 320–8.
10. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of

irritable bowel syndrome: guidelines for effective dietary management. *J Am Diet Assoc* 2006; **106**: 1631–9.
11. Halmos E, Power V, Shepherd S, Gibson P, Muir J. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* 2014; **146**: 67–75.
12. Marsh A, Eslick EM, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. *Eur J Nutr* 2016; **55**: 897–906.
13. Peters S, Muir J, Gibson P. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 1104–15.
14. Whorwell P, Prior A, Faragher E. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet* 1984; **324**: 1232–4.
15. Palsson OS, Turner MJ, Whitehead WE. Hypnosis home treatment for irritable bowel syndrome: a pilot study. *Int J Clin Exp Hyp* 2006; **54**: 85–99.
16. Roberts L, Wilson S, Singh S, Roalfe A, Greenfield S. Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial. *Brit J Gen Pract* 2006; **56**: 115–21.
17. Lindfors P, Unge P, Arvidsson P, *et al.* Effects of gut-directed hypnotherapy on IBS in different clinical settings – results from two randomized, controlled trials. *Am J Gastroenterol* 2011; **107**: 276–85.
18. Moser G, Trägner S, Gajowniczek EE, *et al.* Long-term success of gut-directed group hypnosis for patients with refractory irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol* 2013; **108**: 602–9.
19. Boot WR, Simons DJ, Stothart C, Stutts C. The pervasive problem with placebos in psychology why active control groups are not sufficient to rule out placebo effects. *Perspect Psychol Sci* 2013; **8**: 445–54.
20. Francis C, Morris J, Whorwell P. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* 1997; **11**: 395–402.
21. Spielberger C. *State-Trait Personality Inventory (STPI) Research Manual Sampler Set*. Mind Garden Inc: CA USA, 1995.
22. Snaith R, Zigmond A. *The Hospital Anxiety and Depression Scale Manual*. Windsor, Berkshire: Nfer-Nelson, 1994.
23. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-a review of validation data and clinical results. *J Psychosom Res* 1997; **42**: 17–41.
24. Drossman DA, Patrick DL, Whitehead WE, *et al.* Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. *Am J Gastroenterol* 2000; **95**: 999–1007.
25. Miller V, Carruthers HR, Morris J, Hasan SS, Archbold S, Whorwell PJ. Hypnotherapy for irritable bowel syndrome: an audit of one thousand adult patients. *Aliment Pharmacol Ther* 2015; **41**: 844–55.
26. Chumpitazi B, Cope J, Hollister E, *et al.* Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. *Aliment Pharm Ther* 2015; **42**: 418–27.
27. McIntosh K, Reed DE, Schneider T, *et al.* FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. *Gut* 2016; doi: 10.1136/gutjnl-2015-311339 [Epub ahead of print].
28. Anonymous. Does a low FODMAP diet help IBS? *Drug Ther Bull* 2015; **53**: 93–6.
29. Ledochowski M, Sperner-Unterweger B, Widner B, Fuchs D. Fructose malabsorption is associated with early signs of mental depression. *Eur J Med Res* 1998; **3**: 295–8.
30. Ledochowski M, Widner B, Bair H, Probst T, Fuchs D. Fructose-and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. *Scand J Gastroenterol* 2000; **35**: 1048–52.
31. Simpson H, Campbell B. Review article: dietary fibre–microbiota interactions. *Aliment Pharmacol Ther* 2015; **42**: 158–79.
32. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* 2015; **64**: 93–100.
33. Koven NS, Abry AW. The clinical basis of orthorexia nervosa: emerging perspectives. *Neuropsychiatr Dis Treat* 2015; **11**: 385.