**Individual and group-delivered hypnotherapy in irritable bowel syndrome: a randomised controlled trial.**

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1. Abstract
	1. Background: Hypnotherapy for Irritable Bowel Syndrome (IBS) has been primarily used in patients with refractory symptoms in specialised departments and delivered on an individual basis. The IMAGINE study compares the effectiveness of hypnotherapy for IBS-patients referred from primary and secondary care, delivered in either a group or an individual setting.
		* + 1. **Methods/Design**: In a multi-centre randomised placebo-controlled trial, 354 primary and secondary care patients with IBS, age 18-65, were randomly allocated to either six sessions of individual hypnotherapy, group hypnotherapy or educational supportive therapy in a group (control group). Randomisation was carried out by means of a computer-based, six-block random number table’s procedure performed by staff not involved in the treatment. Outcome measures were assessed prior to treatment, immediately after treatment (at three months) and at 12 months (nine months after finishing the treatment). Primary outcome parameter was the responder rate for adequate relief (AR) of IBS symptoms. Trial register: Current Controlled Trials. Registration number: ISRCTN22888906
				2. **Results**: At three months, 40.2% of patients in the individual hypnotherapy group, 34.1% in the group hypnotherapy group, and 17.1% in the educational supportive group were responders on the primary outcome, the AR questionnaire. At 12 months the figures were 41.8%, 50.0%, and 22.6% respectively. In the intention to treat analysis (ITT), hypnotherapy was more effective than EST, both at three months (OR 2.9, 95%CI 1.2 to 7.4, p=0.02) and at 12 months (OR 2.8, 95%CI 1.2 to 6.7, p=0.02). Per protocol analysis did not show significant differences between individual and group hypnotherapy**.** The reported serious unexpected serious adverse reactions were judged by the Medical Ethics committee as not being related to the therapy.

**Conclusion**: Both individual and group hypnotherapy resulted in significantly greater adequate relief of symptoms compared to control treatment. Furthermore, group therapy was not significantly inferior to individual treatment, which would allow many more patients to be treated for the same cost.

**Funding:** there was no funding for this research.

**Research in context:**

**Evidence before this study**

* The effectiveness of hypnotherapy in IBS has been demonstrated but mainly for patients with refractory symptoms, delivered in specialized departments, in an individual setting.
* Systematic reviews and meta-analysis describe the evidence as still limited due to methodological shortcomings and recommend further investigation with high quality trials with long-term follow-up, especially with regard to its efficacy in a primary care setting.

(for the sources, see the design article of the Imagine study)

**Added value of this study**

* For primary and secondary care IBS patients, hypnotherapy results in significant adequate relief of their complaints.
* Group hypnotherapy is not inferior to individual hypnotherapy.

**Implications of all the available evidence**

* Hypnotherapy gives adequate relief of IBS complaints, not only for refractory patients in tertiary care, but also for patients from primary and secondary care
* Hypnotherapy can be considered as a treatment option for all patients with IBS, irrespective of symptom severity and IBS subtype
* Group delivery may facilitate widespread use of hypnotherapy in daily practice.
1. Introduction
2. Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, characterised by recurrent episodes of abdominal pain, discomfort and altered bowel habits in the absence of structural or biochemical abnormalities.1 The diagnosis is based upon consensus-based criteria, the most recent are the Rome IV criteria.2 Patients with IBS can experience incapacitating symptoms leading to impaired quality of life3 resulting in a substantial economic burden on society.4-6 Pharmacotherapy has limited effectiveness, although the antibiotic rifaximin, anti-spasmodics, peppermint oil, anti-depressants, alosetron , linaclotide and lubiprostone may be effective in some patients.7 Psychological interventions have been shown to be effective, but their application is limited by the lack of trained therapists.7,8
	* + - 1. Since 1984, there has been increasing interest in the use hypnotherapy for IBS.9 Meta-analyses of studies in secondary and tertiary care suggest effectiveness, but more high-quality trials are needed, including primary care patient groups, before firm conclusions can be drawn.7,10,11
				2. Despite its reported effectiveness, hypnotherapy has not yet been widely adopted. This may be partly because it is usually delivered on an individual basis which limits the number of patients that can be treated. In addition it is considered to be mainly useful for refractory patients, mostly from tertiary care. 12-14 Group application could make hypnotherapy suitable for broader application, once demonstrated to be as effective as individual sessions, also in primary care. To date, there has only been one direct comparison of group versus individual hypnotherapy which suggested no difference in effectiveness. However, the study involved only 33 patients referred from secondary and tertiary care.15
				3. We designed a randomised controlled trial (RCT) to assess the effectiveness of hypnotherapy delivered on a group or individual basis in primary and secondary care IBS patients and compared it to a control group receiving educational supportive therapy.16 We hypothesised that hypnotherapy would be more effective than educational supportive therapy and that hypnotherapy in a group setting would not be inferior to individual therapy.
3. Methods
	1. Study design and participants
		* + 1. Design was a non-inferiority 12-week controlled parallel-group randomised clinical trial with three arms. Details on the study design are reported elsewhere.16 Trial register: Current Controlled Trials. Registration number: ISRCTN22888906

The study population consisted of patients with IBS aged between 18 and 65 years referred by primary care physicians and hospital specialists from 13 hospitals in the Netherlands. All patients met the Rome III criteria for IBS, confirmed by the Dutch version of the IBS Module from the Rome Foundation17 officially translated by two authors (Carla Flik (CF) and Yanda van Rood (YvR)). Patients with insufficient command of the Dutch language, those unwilling to participate in group sessions, with a psychiatric condition that requires additional treatment first (for example severe depression, PTSS or psychosis), with comorbid chronic bowel diseases, and/or a history of major gastrointestinal surgery or radiotherapy were excluded.

* 1. Randomisation and masking
		+ - 1. After an intake session with the hospital-based psychologist/hypnotherapist, in which inclusion and exclusion criteria were checked and informed consent was signed, patients were randomly allocated to one of three study arms: (1) individual hypnotherapy (IHT), (2) group hypnotherapy (GHT), or (3) control intervention with educational supportive therapy (EST). Randomisation with a ratio of 3:3:1 (see sample size calculation) was carried out by means of a computer-based, six-block random number table’s procedure performed by staff not involved in the treatment. As group treatment required six patients, randomisation was done block-wise to prevent prolonged waiting time for the individual patient.
				2. **Procedures**
				3. For IHT, patients were offered six bi-weekly 45-minute sessions in which they received hypnotherapy following
				4. a structured protocol with the same content for each session. After introduction and explanation of the therapy, the first step was the hypnotic induction, followed by suggestions, illustrated by images described in the protocol, to normalise motility of the gut and reduce pain and feelings of discomfort. Finally possible questions concerning the hypnotic process were discussed and the importance of practising the exercises at home was emphasised. The treatment procedure was developed by the investigator (CF) based on the Manchester protocol for hypnotherapy in IBS previously developed and validated by Whorwell *et al.*18 In GHT, patients participated in six bi-weekly 60-minute group sessions, with six IBS patients per group. The same protocol as the individual hypnotherapy was used. Both patient groups were given homework assignments consisting of CD-recorded hypnotherapeutic exercises that required 15-20 minutes daily. In 2009 a pilot study was done in one of the collaborating hospitals, in which 32 patients with IBS received the gut-directed hypnotherapy according to the manual either in group sessions or on an individual basis. The manual was found applicable, and group treatment was not inferior to individual treatment (results not published).
				5. Group and individual hypnotherapy were given by the same therapists. All therapists were qualified psychologists who were trained as hypnotherapists, but without specific experience with IBS patients. Before the start of the study they were instructed on the intervention by one of the authors (CF).
				6. According to earlier recommendations, optimal control interventions for the evaluation of psychological therapies require a comparable number of contacts and lengths of sessions with the therapist as the treatment under study, and content that is relevant for patients.19 We developed an EST consisting of six bi-weekly 60-minute group sessions, with six IBS patients per group. This EST was designed on basis of existing literature on the knowledge and educational needs of IBS patients.20-23 An extensive general explanation on IBS was given, the complaints, thoughts about the complaints, coping mechanisms, limitations, avoidance behavior and the relation with the social environment concerning the complaints, were discussed. Information on dietary aspects of IBS was given according to the NICE guidelines.11 An explanation on the benefits of exercise for the IBS complaints was discussed and an explanation of the stress system was given and ways of coping were discussed Homework assignments were provided, requiring 15-20 minutes per day. EST was provided by nurse practitioners or psychological assistants who were specifically trained by the author (CF) for the control intervention.
				7. Patients were allowed to continue medical care but were asked not to change medication during participation, except on their doctor's advice.
				8. Enrolment started May 2011 and ended in April 2016. Prior to intervention the secondary outcome measures were assessed at baseline. After the active treatment period of three months, the primary and secondary outcome measures were assessed. Nine months after end of the intervention, 12 months from baseline, the primary and secondary measures were re-assessed.
1. Outcomes
	* 1. Primary outcome
			+ 1. In line with previous recommendations on optimal outcome assessment in trials on functional gastrointestinal disorders, we chose adequate relief (AR) of IBS symptoms as the primary outcome.24,25 AR is a validated outcome in IBS research, consisting of a single question ("Did you have adequate relief of IBS related abdominal pain or discomfort in the past week? (Yes/No)"). 26 The question was asked once weekly during four consecutive weeks.26,27 A responder was defined as a patient answering "yes" three or four out of four weeks.
		2. Secondary outcomes
			1. Irritable Bowel Syndrome Symptom Severity
				1. IBS symptoms were measured using the IBS-symptom severity score (IBS-SSS), a validated instrument assessing five features (pain severity and frequency, abdominal distension, bowel satisfaction, and interference with life in general) and their intensity, using visual analogue scales.28
			2. Irritable Bowel Syndrome Quality of Life
				1. Disease-specific quality of life was assessed using the Irritable Bowel Syndrome Quality of Life scale (IBS-QOL).29 This scale has been validated in various populations and includes 30 items on nine scales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexuality, relationships, and an overall scale. The sum score is used as outcome.
			3. Psychological symptoms
				1. Psychological symptoms were assessed with the Dutch version of the Symptom Checklist (SCL-90).30,31 The SCL-90 is a 90-item multidimensional self-reported inventory, to evaluate psychological problems and psychopathology on nine subscales: agoraphobia, anxiety, depression, somatisation, insufficiency of thought and action, distrust and interpersonal sensitivity, hostility, sleeping problems, and psychoneuroticism (total score). The sum score is used as outcome. The SCL-90 is a validated and widely used questionnaire with good psychometric qualities.30
			4. Dysfunctional cognitions
				1. The Cognitive Scale for Functional Bowel Disorders (CS-FBD) has been developed by Toner.32 The CS-FBD consists of 31 items which measure a patient's level of dysfunctional cognitions concerning his or her IBS. It is a valid and reliable outcome measure scale.32
			5. Self-efficacy
				1. The Self-Efficacy Scale (SES) is a seven-item questionnaire designed to measure the confidence patients have in their capacity to influence their somatic complaints. It was originally developed for patients suffering from chronic fatigue33 and adapted by CF and YvR with permission from the authors.
			6. Costs
				1. The Trimbos/iMTA Questionnaire (TiC-P) measures direct medical costs due to healthcare utilisation for psychiatric illness during the past four weeks and indirect nonmedical costs due to productivity loss during the past two weeks.34 For the purposes of this study it was adapted for use in IBS. Direct medical costs included the total costs for visits to the primary care doctor and specialist and the costs for medication in the past four weeks.
			7. Other study parameters
				1. Patients were requested to record the number of times they used the CD or did the hypnotherapeutic exercises in the last week for 52 consecutive weeks.
2. Sample size calculation
	* + - 1. For the comparison between hypnotherapy and EST we assumed a 32% difference between hypnotherapy and control intervention, based on an earlier reported response rate for individual hypnotherapy of 57%10 and a placebo response rate of 25%.35 Powering the study for only this comparison would require 44 patients in both arms, assuming an alpha of 0.05, a power (1-beta) of 0.80, a cluster size of six patients per therapist, and an intra-class correlation coefficient of 0.05.
				2. For the second comparison on non-inferiority between group and individual hypnotherapy the maximum acceptable difference for non-inferiority was set on 15%. With an alpha of 0.05 and power (1-beta) of 0.80, 135 patients in both arms were required to demonstrate that GHT is not inferior to IHT. Combining the sample size of both comparisons, assuming 10% loss to follow-up, using six patients per group, inclusion of a total of 354 patients (150 (42.4% IHT) +150 (42.4% GHT) +54 (15.3% EST)) was required.
3. Statistical analysis
	* + - 1. The analysis of the first question (hypnotherapy versus control group) was performed based on the intention to treat (ITT) principle. In line with the recommendations from the CONSORT statement, analysis of the second comparison on non inferiority was based on the per protocol (PP) principle.36
				2. The primary outcome (AR) at both three and 12 months was analysed with logistic regression, incorporating a residual covariance (i.e., Generalised Estimated Equations (GEE) type) matrix in the regression model to correct for repeated measurements.37 Under the presumption of non-inferiority between IHT and GHT, we analysed the combined results of IHT and GHT versus EST, reporting the odds ratios (with 95% CIs and p-values). To evaluate the non-inferiority hypothesis, we estimated the proportion of AR (with 95% CIs) within each group.
				3. Secondary continuous outcomes at three and 12 months were analysed with a linear regression model that also incorporated a residual covariance matrix. From these models, we estimated the mean of the outcomes for all treatment groups and differences between these means, all with 95% CIs. In all analyses, we included the time of visit (three months and 12 months), the type of treatment (IHT, GHT, or EST), and the time of visit by treatment interaction. Visit by treatment interactions were included to obtain the comparison between treatment groups for each visit separately. Baseline measurements, available for all secondary outcomes, were included to correct for any imbalance between groups and to optimise power.
				4. Based on Gonsalkorale *et al.*12, we performed an additional analysis to evaluate the effect of the treatment for different types of IBS (constipation-predominant, diarrhoea-predominant, and mixed type). Additionally, we performed analyses for subgroups according to referral (general practitioner or hospital specialist) and symptom severity (IBS-SSS).
				5. Subsequently, we performed an additional analysis to evaluate any potential bias due to missing outcome measurements. In line with recent recommendations, we performed analyses for primary outcome with correction for IBS-QOL, SCL-90, and IBS-SSS at baseline.38
				6. We observed few missing values on baseline measurements, mainly due to patients skipping individual questions in otherwise completed questionnaires. To avoid any risk of bias and loss of statistical power, we decided to use multiple imputation techniques.38,39 No outcome measures were imputed. Missing data were imputed 10 times, when applicable, analyses were performed for each imputation separately. The results were pooled with Rubin's rule. Multiple imputation was performed with SPSS 21. All analyses were performed with SAS v9.4.40
4. Funding source

There is no funding source for this research. The corresponding author had full access to all of the data and the final responsibility to submit for publication

1. Results
	1. Patients
		* + 1. Between May 2011 and April 2016, 494 patients referred for hypnotherapy were assessed for eligibility. Of these, 140 (28.3%) patients were non-eligible:81(16.4%) patients refused participation, 16 (3.2%) patients did not meet the Rome III criteria, five (1.0%) patients had insufficient command of the Dutch language, one (0.2%) patient refused group treatment, 25 (5.1%) patients had a psychiatric condition, seven (1.4%) patients had co morbid bowel disease, and five (1.0%) patients had had major surgery to the lower gastrointestinal tract. The resulting 354 patients were allocated to IHT (N=150, 42.4%), GHT (N=150, 42.4%), and EST (N= 54, 15.3%) (see flowchart in Figure 1). Before the study started, 13 hospitals had offered their cooperation. For various reasons, 11 hospitals included patients for the trial (for a list of cooperating hospitals, see appendix page 1). The four psychological practices in primary care reported, before the trial started, that they did not get enough referrals from general practitioners to form groups of patients needed in the trial. Therefore they were advised to refer eligible patients to the clinical psychologists in the participating hospitals.
				2. Of those randomised, eight (2.3%) patients (six (1.7%) in IHT and two (0.6%) in GHT) had to be excluded from analysis because after randomisation they were diagnosed with a somatic disease explaining their symptoms (one (0.3%) colorectal cancer, one (0.3%) pancreatic cancer, two (0.6%) inflammatory bowel disease, one (0.3%) neuralgia, and two (0.6%) unknown other disease)41. Four (1.1%) patients were excluded after randomisation because in retrospect the participants were older than 65 years (two (0.6%) in IHT and two (0.6%) in GHT), resulting in a total number of 342 (96.6%) patients for ITT analysis: 142 (40.1%) patients in the IHT group, 146 (41.2%) in the GHT group, and 54 ( 15.3%) in the EST group.
				3. Of the 300 patients that were randomised to hypnotherapy, seven (2.3%) in IHT and 12 (4.0%) in GHT group did not start the therapy for various reasons, in the EST group this were eight (2.7%) patients (see Figure 1).
				4. Of the 135 patients that started IHT, 120 (88.9%) completed it. In the GHT group, 134 patients started with the therapy and 124 (92.5%) completed it. In the EST group, 46 patients started with the therapy and 43 (93.5%) completed it. The drop-out rate during therapy was 15.5%, 15.1%, and 20.3% for IHT, GHT, and EST respectively. The baseline characteristics of all patients are shown in Table 1. There were no significant differences between groups. The patients' compliance in reporting the use of the CD was low. After 12 months, only 44 (14.0%) patients of those who started therapy returned their list of CD use, which was considered insufficient for analysis.
				5. The reported serious unexpected serious adverse reactions were judged by the Medical Ethics committee as not being related to the therapy.
				6. **Primary outcome**
				7. At the end of therapy, after three months, AR questionnaires were available for 102 of the IHT patients (75.6% of those who started therapy), 92 of the GHT patients (68.7%), and 35 of the EST patients (76.1%). Of these patients, 40.2% in the IHT, 34.1% in the GHT, and 17.1% in the EST groups were responders. AR results at twelve months were available for 91 IHT (67.4% of those who started therapy), 80 of the GHT (59.7%) and 31 of the EST patients (67.4%). Of these, 41.8%, 50.0%, and 22.6% respectively, were responders (see Figure 2 and Table 2A). In ITT analysis, the responder rate was 40.8% (95%CI 31.7 to 50.5%) in the IHT and 33.2% (95%CI 24.3 to 43.5%) in the GHT intervention arm at three months. At 12 months, 40.8% (95%CI 31.3 to 51.1%) of IHT and 49.5% (95%CI 38.8 to 60.0%) of GHT patients reported AR. Treatment response was significantly better in both hypnotherapy groups (odds ratio (OR) 2.9 (95%CI 1.2 to 7.4)), and after 12 months (OR 2.8 (95%CI 1.2 to 6.7)) (table 3). The number needed to treat for hypnotherapy was 4.9 after three months and 4.4 after 12 months. In PP analysis, the responder rate was 49.9% (95%CI 39.2 to 60.6%) in the IHT and 42.7% (95%CI 32.3 to 53.8%) in the GHT intervention arm at three months. At 12 months, 55.5% (95%CI 43.4 to 67.1%) of IHT and 51.7% (95%CI 40.2 to 63.0%) of GHT patients reported AR. Treatment response did not differ between individual and group hypnotherapy, neither at three months (OR 1.3 (95%CI 0.7 to 2.4)), nor at 12 months (OR 0.7 (95%CI 0.4 to 1.2)) (Table 3).

Secondary outcomes

* + - * 1. Patients in all three groups improved in IBS symptomatology, quality of life, psychological complaints, IBS related cognitions, and self-efficacy, with slightly better outcomes for the hypnotherapy treatments (Table 2A). In all groups the total medical costs diminished between baseline and 12 months. At three and 12 months patients in all groups reported less IBS related work absence, less work hindrance and a better work efficiency, with no significant differences between groups (Table 2B). However, in ITT analysis no significant differences between the combined hypnotherapy treatments and placebo control condition were found (Table 4) and PP analysis showed no differences between the mean scores at three and 12 months in the two hypnotherapy groups (Table 5).
	1. Subgroup analyses
		+ - 1. Patients referred from secondary care had a higher chance of being a responder after hypnotherapy compared to those referred from primary care, both at three months and at 12 months (Table 6). Additional analysis showed that the two groups did not differ in IBS subtype, nor in IBS-SSS, IBS-QOL scores at baseline and at three and 12 months, but patients included from secondary care had significantly higher scores on the SCL-90 subscales somatisation, insufficiency of thought and action, distrust, and interpersonal sensitivity (see appendix, page 2).
				2. In the subgroup analysis according to IBS symptom severity and IBS subtypes, no statistically significant differences in treatment effect were found for primary and secondary outcome measures at both points in time (Table 6).
1. Discussion
	1. Principal findings
		* + 1. For IBS patients referred from primary and secondary care, three months of treatment with hypnotherapy was more effective than an educational control intervention. In addition, hypnotherapy delivered in a group format proved equally effective as individually delivered hypnotherapy. Differences in treatment effect persisted after nine months of follow-up.
				2. Patients in both hypnotherapy and in EST all improved in quality of life, psychological complaints, cognitions, and self-efficacy and direct and indirect costs diminished, but between groups differences were not significant.
				3. Treatment effects were more pronounced in patients referred from secondary care, who appeared to have higher psychological problem scores. We found no significant differences between subgroups according to symptom severity and IBS subtype.
	2. Strengths and limitations
		* + 1. To our knowledge, this is the largest RCT on hypnotherapy for IBS to date.7,10 Whereas previous studies may have suffered from a lack of heterogeneity among IBS patients, potentially affecting the generalisability of the results42, patients included in our study were recruited from both primary and secondary care across the Netherlands.
				2. In this trial, we did not only assess the effectiveness of hypnotherapy compared to a high-quality control intervention, but also tested whether group-delivered hypnotherapy was not inferior to individual delivered therapy. Given the lack of therapists this may facilitate broader implementation of hypnotherapy in daily clinical practice. Also we were able to demonstrate that the superiority of hypnotherapy over educational intervention persisted at 12 months.
				3. We chose the AR questionnaire as primary outcome measure, as this subjective outcome adequately reflects the impact of IBS symptoms in individual patients, independent of symptom severity. In functional disorders the perception of symptoms is as important as actual symptom severity.43 This is supported by the results of our trial, where better adequate relief scores were not accompanied with a significantly different improvement in IBS symptom score. The explanation may be that – in contrast to education – hypnotherapy does particularly improve the perception of IBS symptoms, without having a major effect on symptom severity.44 Thus, the main effect of hypnotherapy may be diminishing symptom impact by changing the mind-set and improving the internal coping mechanism
				4. In our study, we used a well-designed control intervention. In line with recommendations we constructed an intervention that lacked hypnotherapy but was comparable for all other treatment components: time, attention, active intervention, and contact with therapist.15,45,46 This informative educational program covered relevant topics and information gaps of IBS patients.20-23
				5. Our study had several limitations. This study was embedded in routine clinical practice. This increases the validity and generalisability of the results, but also affected the conduct of the study. In four cases (1.1%) the inclusion proved incorrect, and in eight cases (2.3%) the diagnosis of IBS appeared to be incorrect post-hoc. This figure is within the normal range of percentages found in patients with IBS, of other gastro-intestinal diseases causing the symptoms. (reference Dutch Multidisciplinary Guideline).48
				6. The presumptions used for the power calculation may have been suboptimal. The presumed hypnotherapy response rate may have been too high and the response estimate of the response in the control group too low, based on the results of a larger study on placebo effects.47 Additionally 27 patients (7.6% overall) withdrew from the intervention after randomisation (Figure 1) and a substantial number of the questionnaires sent out after three and 12 months were not returned. Therefore, in line with existing recommendations, we imputed missing (baseline) data and performed extensive sensitivity analyses to ensure the validity of the results.38 Even though results from these analyses were very similar, a bias due to withdrawal and non-response, especially for the non-inferiority comparison, cannot be fully excluded.
				7. We did not assess expectations and hopes of patients regarding the therapy before commencing it. The effect of treatment is determined to a large extent by the combination of expected symptom relief and desire for symptom relief by the patient.49,50 For optimal comparison in studies investigating psychological treatment for IBS, the expectations of patients in the control group should be comparable to those of patients in the active intervention arm. We suggest that future RCTs should map the expectations of patients in all RCT arms before starting the intervention.
	3. Comparison with other studies

In our study, we chose the number of weeks with adequate symptom relief as the primary outcome. Previous studies that used the IBS-SSS as primary outcome measure reported greater therapeutic effects on IBS symptomatology compared to ours: changes from 338 to 158, from 329.2 to 165.4, 259 to 196 and 317.8 to 189.0 respectively.12, 14,47,48 In our study these figures were 293.0 to 254.3 after 3 months and 234.8 after 12 months. One study reported a reduction of 50 points or more on the IBS-SSS after treatment in 76% of the patients.14 Possible explanations may be differences in patient selection. While previous studies used Rome I criteria (1990), or Rome II criteria (1999), we used the Rome III criteria (2006), which require fewer days with complaints to set the diagnosis.51 In addition, most previous studies have been undertaken in tertiary care where starting symptom scores have been higher and there is some evidence that patients with higher scores respond better. An earlier study in primary care IBS patients, who received five sessions of hypnotherapy in addition to usual management, found no significant difference in symptoms or quality of life over 12 months in comparison with usual management only.52 However, despite the lack of symptom improvement a majority of patients in the intervention group reported an improvement in their condition. In a second study, in which patients from secondary care either received 12 sessions of hypnotherapy or were placed on a waiting-list, the two groups did not differ significantly at 3 months with regard to symptoms or quality of life.53 In this study, the hypnotherapy patients also reported a very positive experience in general well-being and better coping with their symptoms. The results of our trial confirm this observation that in primary and secondary care, despite the absence of effect on IBS symptoms, IBS patients do experience generalised improvement from hypnotherapy. This may be explained by the fact that, in contrast to the more severe tertiary care patients, in IBS patients from primary and secondary care, hypnotherapy results in a more positive experience in terms of a better coping style, while the actual symptom severity doesn’t change.

* + - * 1. In three studies therapy consisted of 12 hypnotic sessions12,14,54, one study55 used seven sessions and in our study six sessions were used. In addition, in the Manchester group therapists have more than five years' experience with IBS focused hypnotherapy, while in our study most of the hypnotherapists did not have specific experience with IBS.14  Although the hypnotherapists were experienced clinical psychologists who were trained by the principal investigator in gut directed -hypnotherapy , according to a standardised manual, it cannot be excluded that to the relative lack of experience of the therapists did result in an underestimation of the impact of hypnotherapy. There is reasonably good evidence to suggest that hypnotherapy is effective in the refractory group of IBS patients seen in tertiary care and the UK National Institute for Health and Care Excellence (NICE) recommends this form of treatment in patients not responding to pharmacological and dietary interventions. Within this group of tertiary care patients, those with higher symptom severity scores tend to respond better and this is probably because such patients have a much more complex form of the disorder with additional psychological factors contributing. Furthermore, these patients are more likely to fully engage in this time-consuming form of treatment, which is often perceived as their last chance to improve. It is, therefore, perhaps not surprising that hypnotherapy was not so effective in the current study were patients were not so complex. The SCL-90 scores of the patients in our study were on the average level of patients in general practice31, so the psychological status was that of the consulting population in primary care. Compared to mean scores of psychiatric patients, all three groups had below average scores on most SCL-90 dimensions, except for the "somatic scale" and for "sleep disturbance". The high somatisation score was previously reported in a systematic review.56 In the SCL-90 as well as in the other secondary outcomes, the lack of significantly greater improvement in the hypnotherapy group, can possibly be ascribed to lower scores at baseline on these questionnaires.

Some earlier studies on group hypnotherapy demonstrated better results.16,55,57 We think that this may be related to the fact that we adhered strictly to practicing the hypnotherapy exercises while others combined hypnotherapy with the opportunity to discuss questions as well as share information about IBS. It might well be that education on IBS and hypnosis both independently contribute to the treatment effect. In clinical practice a stepped-care approach, in which patients receive education as a first and hypnosis as second step, could be the way to further optimise the treatment effect.

* + - * 1. In the subgroup analysis, we found a difference in effect between patients referred by a specialist and those referred by their general practitioner. Additional analysis suggested a difference in psychological complaints between the groups, but not in symptom severity. Whitehead *et al*. (2002) suggested a dual-aetiology hypothesis, which divides the IBS patients in "those whose symptoms primarily have a biological basis and others whose symptoms primarily have a psychological basis".58 Possibly hypnotherapy works best for patients with more psychological complaints. In future research on the effect of hypnotherapy, stratification according to psychological symptoms should be considered.
1. Conclusion

 Using a global outcome measure, this study has shown that both individual and group hypnotherapy are significantly more effective than control treatment, although all three treatments reduced symptom severity. This observation highlights the complexity of IBS symptomatology where the patient’s perception of their illness has a marked effect on their suffering. In addition, we have shown that group hypnotherapy is not significantly inferior to individual treatment making it a practical proposition for use in primary care.

Future research should focus on the optimal number of sessions, on the impact that the patient's expectations have on the final outcome, and on the predictive value of psychological symptoms for the outcome of hypnotherapy.

1. Authors’ contributions:
2. CF and NdW developed the original idea for the study. All authors contributed to the developing of the study protocol. WL substantially contributed to randomisation and the statistical methods. CF developed the verbatim hypnotherapy-protocol on basis of the protocol of PW and the Educational supportive therapy in close collaboration with YvR. All authors participated in the design of the study and development of research protocols. All authors contributed to and approved the final manuscript.
3. All authors had full access to all of the data ( including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.
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7. All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure](http://www.icmje.org/coi_disclosure) pdf and declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years ; no other relationships or activities that could appear to have influenced the submitted work.
8. Ethical approval:
9. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Utrecht, the Netherlands (approval number: 10-201/O).All participants gave informed consent before taking part.Patient data were coded and analysis was done blinded.
10. Data sharing:
11. The relevant anonymised patient level data are available on reasonable request from the authors. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.
12. Transparency:
13. The lead authors affirm that the manuscript is an honest , accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned ( and if relevant, registered) have been explained.
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17. References
	1. Guthrie E, Thompson D. ABC of psychological medicine: Abdominal pain and functional gastrointestinal disorders. BMJ. 2002 Sep 28;325(7366):701-3.
	2. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simrén M, Spiller R Bowel disorders. Gastroenterology. 2016;150:1393-1407.
	3. Ten Berg MJ, Goettsch WG, van den Boom G, Smout AJPM, Herings RMC. Quality of life of patients with irritable bowel syndrome is low compared to others with chronic diseases. Eur J Gastroenterol Hepatol. 2006;18:475-481.
	4. Maxion-Bergemann S, Thielecke F, Abel F & Bergemann R. Costs of irritable bowel syndrome in the UK and US. Pharmacoeconomics. 2006;24:21-37.
	5. Inadomi JM, Fennerty MB & Bjorkman D. Systematic review: the economic impact of irritable bowel syndrome. Aliment Pharmacol Ther. 2003;18:671-682.
	6. Flik CE, Laan W, Smout AJPM, Weusten BLAM, de Wit NJ. Comparison of medical costs generated by IBS patients in primary and secondary care in the Netherlands. BMC Gastroenterology. 2015;15:168.
	7. Ford AC, Quigley EM, Lacy BE, et al*.* Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol. 2014;109:1350-1365.
	8. Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quartero AO. Psychological treatments for the management of irritable bowel syndrome. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006442.
	9. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. Lancet. 1984;2:1232-39.
	10. Webb AN, Kukuruzovic RH, Catto-Smith AG, Sawyer SM. Hypnotherapy for treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2007 October 17; (4):CD005110.
	11. National institute for Health and Clinical Excellence. Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. Clinical practice guideline Irritable bowel syndrome in adults. 2008 ed. 2010; p. 374-464.
	12. Gonsalkorale WM, Houghton LA, Whorwell PJ. Hypnotherapy in irritable bowel syndrome: a large-scale audit of a clinical service with examination of factors influencing responsiveness. Am J Gastroenterol. 2002 Apr;97(4):954-61.
	13. Palsson OS, Turner MJ, Johnson DA, Burnett CK, Whitehead WE. Hypnosis treatment for severe irritable bowel syndrome: investigation of mechanism and effects on symptoms. Dig Dis Sci. 2002;47:2605-14.
	14. 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;41:844-855.
	15. Harvey RF, Hinton RA, Gunary RM, Barry RE. Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome. Lancet. 1989 Feb 25;1(8635):424-5.
	16. Flik CE, van Rood YR, Laan W, Smout AJPM, Weusten BLAM, Whorwell PJand de Wit NJ. A Randomised Controlled Trial on hypnotherapy for Irritable Bowel Syndrome: design and methodological challenges (the IMAGINE study) BMC Gastroenterol. 2011;11:137.
	17. Rome Foundation http://www.romecriteria.org/translations. Dutch version approved 16-2-2011
	18. Gonsakorale WM: Gut-directed hypnotherapy: the Manchester approach for treatment of irritable bowel syndrome. Int J Clin Exp Hypn. 2006;54(1):27-50.
	19. Baskin TW, Tierney SC, Minami T, Wampold BE. Establishing specificity in psychotherapy: a meta-analysis of structural equivalence of placebo controls. J Consult Clin Psychol. 2003;71:973-979.

20 Halpert A, Dalton CB, Palsson O, Morris C, Hu Y, Bangdiwala S, Hankins J, Drossman DA. What patients know about irritable bowel syndrome (IBS) and what they would like to know. National Survey on Patient Educational Needs in IBD and development and validation of the Patient Educational Needs Questionnaire (PEQ). Am J of Gastr 2007; 102:1972-82.

* 1. Lacy BE, Weiser K, Noddin L, Robertson DJ, Crowell MD, Parrett-Engstrom C, Grauss MV. Irritable bowel syndrome: patients' attitudes, concerns and level of knowledge. Aliment Pharmacol Th. 2007:25:1329-41.
	2. O’Sullivan MA, Mahmud N, Kelleher OP, Lovett E, O’Morain CA. Patient knowledge and educational needs in irritable bowel syndrome Eur J of Gasterol & Hepatol. 2000;12:39-43.
	3. Riedl A, Maass J, Fliege H, Stengel A, Schmidtmann M, Klapp BF, Monnikes H. Subjective theories of illness and clinical and psychological outcomes in patients with irritable bowel syndrome. J Psych Res. 2009:67:449-455
	4. Irvine EJ, Whitehead WE, Chey WO, Matsueda K, Shaw M, Talley NJ, Veldhuyzen van Zanten SJ. Design of Treatment Trials for Functional Gastrointestinal Disorders. Gastroenterology. 2006; 130:1538-1551.
	5. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. Am J Gastroenterol. 2003 Jan;98(1):122-7.
	6. Mangel AW, Hahn B, Heath AT, Northcut AR, Kong S, Dukes GE, McSorley D.*.* Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998;
	26:76-81.
	7. Camilleri M, Northcutt AR, Kong S, Dukes GE, Mc Sorley 0, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet. 2000;355:1035-40.
	8. Francis CV, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997 Nov 1;11:395-402.
	9. Patrick DL, Drossman DA, Frederick 10, Dicesare J, Puder KL. Quality of life in Persons with Irritable Bowel Syndrome. Development and Validation of a New Measure. Dig Dis Sci. 1998;43:400-11.
	10. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale-preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.
	11. Arrindell WA, Ettema JHM. SCL-90: Herziene handleiding bij een multidimensionele psychopathologie-indicator. (SCL-90: Revised manual for a multidimensional indicator of psychopathology). Lisse, the Netherlands: Swets & Zeitlinger; 2003.
	12. Toner BB, Stuckless N, Ali A, Downie F, Emmott S, Akman D. The development of a cognitive scale for functional bowel disorders. Psychosom Med. 1998;60:492-7.
	13. Bleijenberg G, Bazelmans E, Prins J. Chronisch vermoeidheidssyndroom: Self-Efficacy Schaal (SES). In: Medisch Centrum St. Radboud Nijmegen aMP, editor. Praktijkreeks Gedragstherapie deel 13. 13 ed. Houten/Diegem: Bohn Stafleu Van Loghum; 2001. p. 102.
	14. Hakkaart-van Roijen L. Handleiding 'TrimbosliMTA questionnaire for Costs associated with Psychiatric iIlness (TiC-P)'. Rotterdam, Institute for Medical Technology Assessment, Erasmus Universitair Medisch Centrum Rotterdam; 2002.
	15. Spiller RC: Problems and Challenges in the Design of Irritable Bowel Syndrome Clinical Trials: Experience from Published Trials. Am J Med. 1999 Nov 8; 107(5A):91S-97S.
	16. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW. Reporting of Noninferiority and Equivalence randomized Trials. An extension of the CONSORT Statement. JAMA. 2006 Mar 8;295(10).
	17. Zeegers LS, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986 Mar;42(1):121-130.
	18. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: how to analyze and what to report. CMAJ. 2014 Oct 21;186(15):1153-1157.
	19. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59:1087-1091.
	20. <https://www.sas.com/en_us/software/sas9.html>. Date 28-2-2018.
	21. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ. 2002;325:652-4.
	22. Longstreth GF, Hawkey CJ, Mayer EA, et al. Characteristics of patients with Irritable Bowel Syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther. 2001; 15:959-964.
	23. Creed F, Ratcliffe J, Fernandez L, Tomenson B, Palmer S, Rigby C, et al*.* Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. Ann Intern Med. 2001;134:860-8.
	24. Price D, Bushnell C, editors. Psychological Methods of Pain Control: Basic Science and Clinical Perspectives. Progress in Pain Research and Management. Seattle: IASP Press; 2004. p. 3-4.
	25. Flik CE, Bakker L, Laan W, van Rood YR, Smout AJPM, de Wit, NJ. Systematic review: The placebo effect of psychological interventions in the treatment of irritable bowel syndrome. World J Gastroenterol. 2017 Mar 28;23(12):2223-2233.
	26. Ford AC & Moayyedi P. Meta-analysis: factors affecting placebo response rate in irritable bowel syndrome. Aliment Pharmacol Ther.2010;32(2):144-158.
	27. Wampold BE, Minami T, Callen Tierney S, Baskin TW, Bhati KS. The Placebo is Powerful: Estimating Placebo Effects in Medicine and Psychotherapy from Randomized Clinical Trials. J Clin Psychol. 2005;61(7):835-854.
	28. Nederlands Huisartsen Genootschap. Diagnostiek en behandeling van het prikkelbaredarmsyndroom. Multidisciplinaire richtlijn 2011.
	29. Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. Pain. 2003;105:17-25.
	30. Kirsch I. Placebo psychotherapy: synonym or oxymoron? J Clin Psychol. 2005;61: 791-803.
	31. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. Am J of Gastroeneterol. 2009;104 (supplement 1)
	32. Roberts L, Wilson S, Singh S, Roalfe A and Greenfield S. Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial. Br J of Gen Pract. 2006:56:115-121.
	33. Lindfors P, Unge P, Arvidsson P, Nyhlin H, Björnsson E, Abrahamsson H, Simrén M. Effects of Gut-Directed Hypnotherapy on IBS in Different Clinical Settings- Results From Two Randomized, Controlled Trials. Am J Gastroenterol. 2012;107:276-285 (study 2).
	34. Gonsalkorale WM. Cognitive change in patients undergoing hypnotherapy for irritable bowel syndrome. J Psychosom Res. 2004 Mar;56(3): 271-27.
	35. Gerson CD, Gerson J & Gerson M. Group hypnotherapy for irritable bowel syndrome with long-term follow-up. Int J Clin Exp Hypnosis. 2013;61(1):38-54.
	36. Sykes MA, Blanchard EB, Lackner J, Keefer L, Krasner S. Psychopathology in irritable bowel syndrome: a support for a psychophysiological model. J Behav Med. 2003;26:361-72.
	37. Moser G, Trägner S, Gajowniczek EE, Mikulits A, Michalski M, Kazemi-Shirazi L, 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; 108:602-609.
	38. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002 Apr;122(4):1140-56.