Long-term Improvement in Functional Dyspepsia Using Hypnotherapy

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See editorial on page 2132.

Background & Aims: **We have shown hypnotherapy (HT) to be effective in irritable bowel syndrome, with long-term improvements in symptomatology and quality of life (QOL). This study aimed to assess the efficacy of HT in functional dyspepsia (FD).** ***Methods:*** **A total of 126 FD patients were randomized to HT, supportive therapy plus placebo medication, or medical treatment for 16 weeks. Percentage change in symptomatology from baseline was assessed after the 16-week treatment phase (short-term) and after 56 weeks (long-term) with 26 HT, 24 supportive therapy, and 29 medical treatment patients completing all phases of the study. QOL was measured as a secondary outcome.** ***Results:*** **Short-term symptom scores improved more in the HT group (median, 59%) than in the supportive (41%; $P = 0.01$) or medical treatment (33%; $P = 0.057$) groups. HT also benefited QOL (42%) compared with either supportive therapy (10% [$P < 0.001$]) or medical treatment (11% [$P < 0.001$]). Long-term, HT significantly improved symptoms (73%) compared with supportive therapy (34% [$P < 0.02$]) or medical treatment (43% [$P < 0.01$]). QOL improved significantly more with HT (44%) than with medical treatment (20% [$P < 0.001$]). QOL did improve in the supportive therapy (43%) group, but 5 of these patients commenced taking antidepressants during follow-up. A total of 90% of the patients in the medical treatment group and 82% of the patients in the supportive therapy group commenced medication during follow-up, whereas none in the HT group did so ($P < 0.001$). Those in the HT group visited their general practitioner or gastroenterologist significantly less (median, 1) than did those in the supportive therapy (median, 4) and medical treatment (median, 4) groups during follow-up ($P < 0.001$).** ***Conclusions:*** **HT is highly effective in the long-term management of FD. Furthermore, the dramatic reduction in medication use and consultation rate provide major economic advantages.**

Functional dyspepsia (FD) and irritable bowel syndrome (IBS) account for more than ½ of the gastroenterologist's workload[1] and are also the most common gastrointestinal problems seen in primary care settings.[2] Although FD and IBS share some clinical features, they can be distinguished symptomatically into 2 distinct entities.[3] There is also probably some overlap in their underlying pathophysiology, with abnormalities of both motility[4] and visceral sensitivity[5,6] likely contributory.

The most recently accepted definition of FD (Rome II) is recurrent (at least 12 weeks/year) epigastric pain with no evidence of organic disease and associated upper abdominal bloating, early satiety, nausea, vomiting, and feelings of fullness.[3] It has been traditional to divide FD into reflux-like, ulcer-like, dysmotility-like, and nonspecific dyspepsia,[7] although the clinical utility of this classification has been questioned.[1] With respect to treatment trials, there is little evidence that subgrouping is helpful,[3] although patients with reflux symptoms are usually excluded.[8]

FD is extremely common, affecting up to 25% of the population.[3,7,9] Unfortunately, there are even fewer effective medications for this condition than for IBS, and those that are used, such as proton pump inhibitors and prokinetics, are expensive. This condition is very costly in both economic and social terms, as a result of these patients consulting frequently[7] and taking time off work.[9] The costs related to FD have recently been estimated to exceed $1.2 billion per year in the United States alone.[1]

We have previously shown that hypnotherapy (HT) is extremely effective in treating IBS, leading to long-term improvement of symptoms and quality of life,[10–12] and

Abbreviations used in this paper: FD, functional dyspepsia; HAD, hospital anxiety and depression; HT, hypnotherapy; IBS, irritable bowel syndrome; QOL, quality of life.

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this has been confirmed by other investigators.[13,14] HT is commonly considered a purely psychotherapeutic intervention; not as well appreciated is the fact that it can also modify processes not usually considered as being under conscious control.[15,16] HT has also been demonstrated to have the capacity to normalize visceral sensitivity and modulate motility in the gastrointestinal system.[17,18]

The aim of this study was to assess the efficacy of HT compared with supportive therapy coupled with placebo medication or with medical management in the short- and long-term treatment of FD. Particular attention was given to controlling for time spent with patients.

Materials and Methods

Patients

All patients attending the endoscopy unit at the University Hospital of South Manchester with dyspeptic symptoms and a negative endoscopy were considered for the study, and those fulfilling the Rome I[19] criteria for FD were recruited. Patients were excluded if they had predominant gastroesophageal reflux-like symptoms, had a history of peptic ulcer disease, or were regularly using nonsteroidal anti-inflammatory drugs. All patients with a history of abdominal surgery, with the exception of appendectomy, cholecystectomy, or hysterectomy more than 1 year previously, were also excluded. Patients with *Helicobacter pylori* infection were also excluded, because the role of this organism in the pathogenesis of functional dyspepsia is still somewhat controversial.[20,21] Patients with concomitant symptoms consistent with IBS were not excluded, provided that their FD symptoms were more predominant. The study was approved by the local ethics committee, and all patients gave written informed consent.

Methods

The study was of a randomized (stratified for gender), controlled, parallel design in which patients were randomly assigned to 1 of 3 groups. Patients underwent a 16-week treatment phase of HT, supportive therapy plus placebo medication or medical treatment with a histamine-2 antagonist (ranitidine 150 mg twice daily), followed by a 40-week follow-up phase during which no further study interventions were undertaken. The active ranitidine, supplied by Glaxo-Wellcome (United Kingdom), was in the form of a white tablet that did not resemble either the over-the-counter or prescription versions of the drug. The treatment phase consisted of 12, 30-minute visits for patients receiving HT or supportive therapy and only 4 visits, to dispense medication, for the patients randomized to medical treatment (Figure 1). Patients were assessed at baseline (week 0) and at weeks 4, 8, 16, 28, and 56 by an independent blind assessor, who was unaware of the treatment randomization. Patients were specifically instructed about the importance of the assessor remaining blind to treatment and were told to avoid mentioning their treatment modality to the assessor and subsequently, during follow-up, to their physicians.

Symptom scores were measured using a variation of a validated symptom scoring system[22] developed in our department for use in IBS. Quality-of-life (QOL) scores were assessed using a QOL instrument validated in affective disorder,[23] modified for use in functional bowel disorders[11] and subsequently used in a number of HT studies, in which it has proven to be sensitive to changes over time.[12,24,25] Patients' anxiety and depression levels were also assessed using the hospital anxiety and depression (HAD) scale[26] at the start and end of the treatment phase only. Furthermore, the economic impact of FD for the year preceding treatment and throughout the study was assessed by recording the number of consultations with a

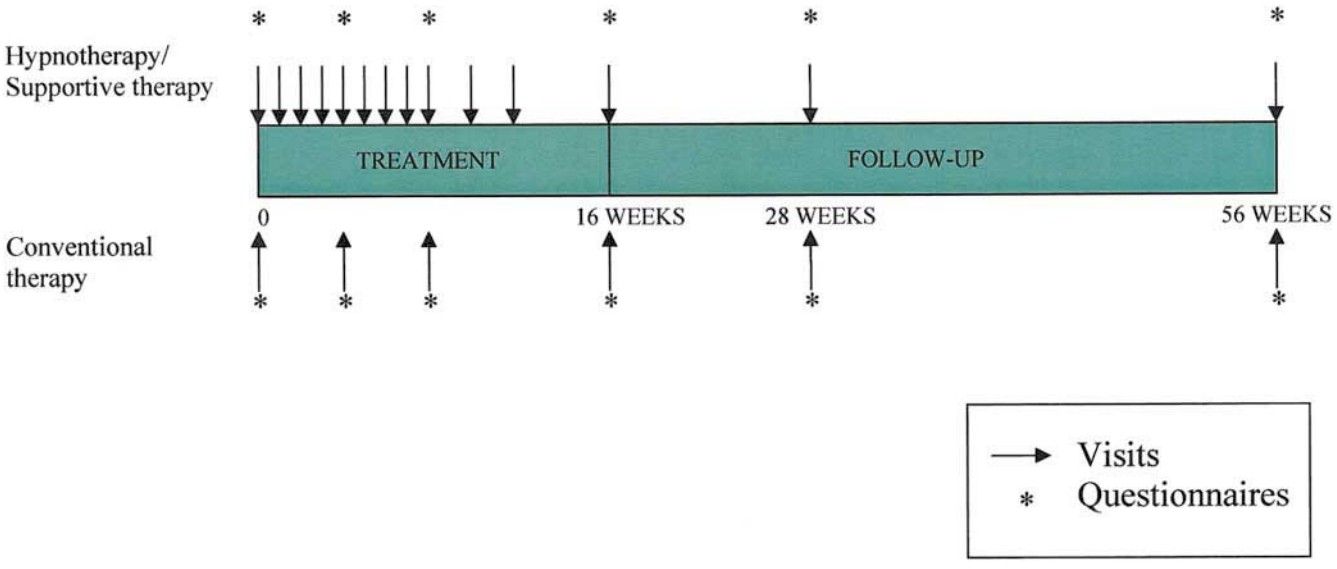

Figure 1. Study protocol. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

general practitioner or physician in the outpatient department, number of clinical procedures, work absences, and inpatient stays. Medication use was also recorded, and prescribing was left entirely to the discretion of the patients' primary care physicians or consultants, who were not involved in the study and were kept blind to the treatment modality.

Hypnotherapy

HT was provided by a qualified therapist as described in detail elsewhere.[27] Briefly, the patients were given a tutorial that included basic pathophysiologic concepts of FD and how HT might be used to treat the condition. Hypnosis was then induced using eye fixation and closure, followed by progressive muscular relaxation and standard deepening procedures. Suggestions of disease improvement were made using both tactile and imagery techniques. The patient was asked to place a hand on the abdomen and imagine a reduction of all symptoms. Suggestions of positive changes in motor activity, sensitivity, and secretion of acid and mucus were also introduced. All of these concepts of improvement were reinforced by any appropriate visualization processes with which the patient felt comfortable.

Supportive Therapy Plus Placebo Medication

This involved an experienced clinical research assistant providing general supportive advice about FD and listening to patients' concerns about the condition. No specific psychologic intervention was undertaken, and sessions lasted exactly the same length of time as those devoted to hypnotherapy. Placebo ranitidine (GlaxoWellcome) was prescribed on a twice-daily basis for the duration of the treatment phase and was in the form of a white tablet that did not resemble either the prescription or the over-the-counter form of this medication. Patients were told that they might be receiving either a placebo or an active form of a drug that might help their condition, was entirely safe, and was not being tested in a clinical trial.

Data Analysis

All symptom (pain severity and frequency, nausea, poor appetite, early satiety, bloating, and belching) and QOL (psychological and physical well-being, mood, locus of control, social relationships, work, hobbies, and finances) measures were assessed using visual analogue scales of 0–10 cm (10 cm being maximum), from which the percentage of the changes from baseline to the end of both the treatment (short-term) and follow-up (long-term) phases were obtained. The primary outcome measure was the percentage change from baseline of the total score derived from the individual symptom measures at the end of the short- and long-term phases. QOL was considered a secondary outcome measure, as were the individual symptom scores and data on health care–seeking behavior and economic functioning.

Statistical Considerations

It was calculated that 17 subjects in each group were needed to achieve an 80% power to detect a significant difference in percentage improvement of 40% between the HT and control groups using a 2-sample t test, assuming that the data followed a normal distribution with a common standard deviation of 40. However, skewness of the data with non-normal distribution was anticipated. Thus a sample size of 25–30 in each group was considered appropriate to adjust for the non-normality of the data and to compare HT with each of the 2 control groups. Assessment of the long-term efficacy of HT was considered a particularly important part of the study that could be compromised if dropouts reduced the size of any of the treatment groups before this phase was established. Therefore, in the event of an unequal dropout rate, the contingency for a process of uneven randomization was adopted, to ensure that similar numbers entered the follow-up phase.

The analysis was performed on an intent-to-treat basis for both the short- and long-term phases of the study, with the last available data for an individual carried forward as an endpoint. Symptom and QOL data followed a non-normal distribution; hence, nonparametric summary statistics (medians and interquartile ranges) were used to describe the data. Short-term and long-term changes between groups using percentage change scores from baseline were assessed using Kruskal–Wallis tests, followed by Mann–Whitney U tests with Bonferroni's correction for multiple group comparisons. P values unadjusted for multiple outcome comparisons are presented. However, as an acknowledgement of the problem of multiple comparisons, only P values < 0.01 were taken to provide reasonable evidence of a difference between groups with respect to individual secondary outcome measures. Comparisons of medication use between groups during the follow-up phase were assessed using χ^2 tests.

Results

Recruitment of patients and their flow through each stage of the study, as recommended by the CONSORT statement,[28] are illustrated in Figure 2. A total of 149 patients were eligible for the study, of which 23 (15%) declined to participate, leaving 126 patients. Of these 126 patients, 32 were randomized to receive HT; 48, to supportive therapy; and 46, to medical treatment. In these groups, 27, 32, and 34 patients, respectively, completed the treatment phase. During the acute phase, 8 (6%) patients (3 in the HT group, 2 in the medical group, and 2 in the supportive group) withdrew before receiving any treatment, 6 (5%) because of the time commitment, and 2 (2%) for other reasons. Another 23 (18%) patients (0 from the HT group, 13 from the supportive group, and 10 from the medical group) withdrew from the acute phase because the treatment was not working ($P < 0.001$ hypnotherapy vs. medical and supportive). Because of the high dropout rates in the 2

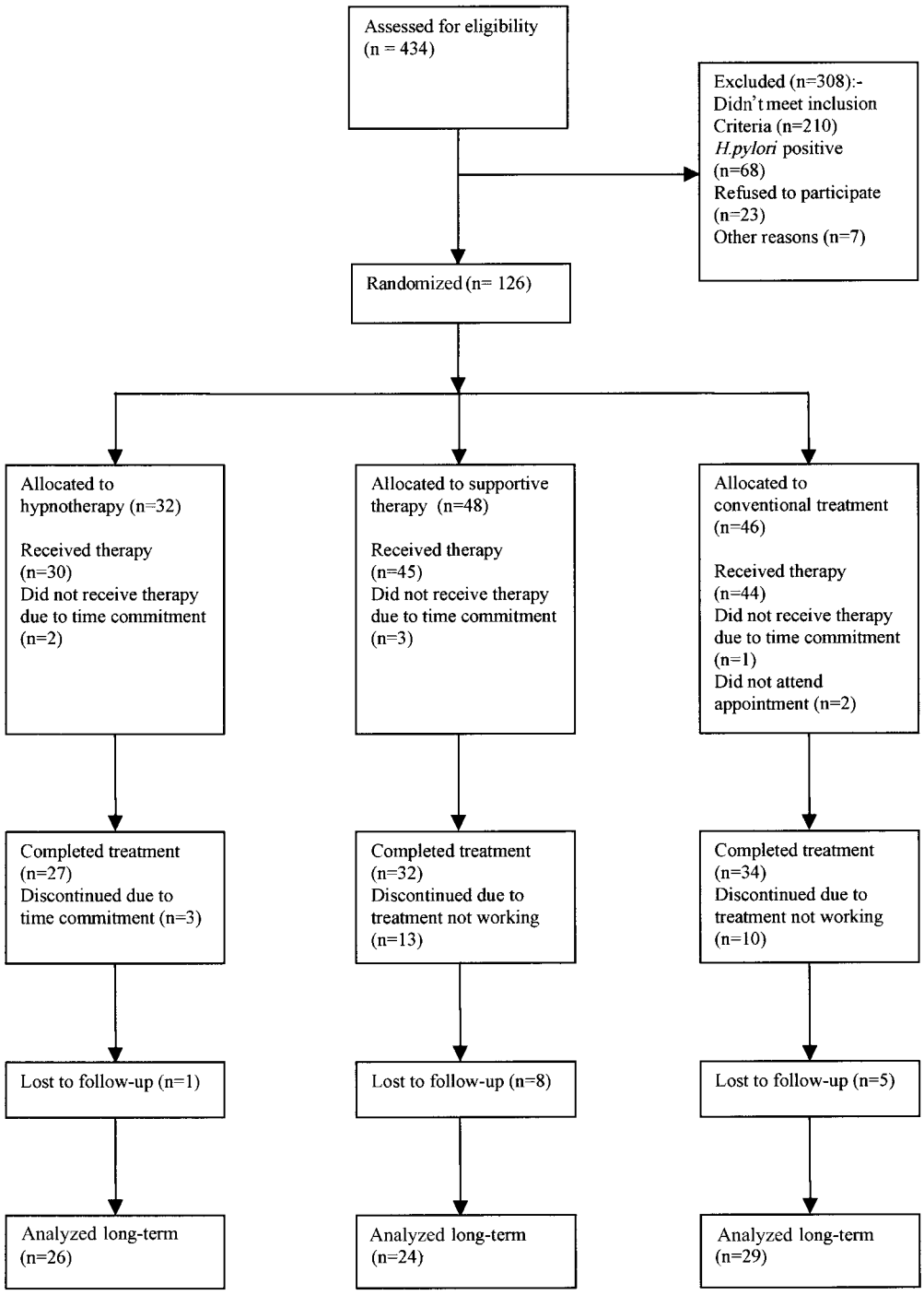

Figure 2. Study flow diagram. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

control groups and to maintain equal numbers of patients entering the follow-up phase of the study, more patients were randomized to receive the control therapies. Fourteen (11%) patients were lost during the follow-up phase.

Baseline Symptom and Quality-of-Life Data

Table 1 summarizes the initial total symptom and QOL scores and their individual components for each group. To control for any variations in scores, percentage change rather than actual score was used for statistical comparisons. Table 2 gives the actual scores obtained for total symptoms and QOL at baseline, the end of treatment, and follow-up.

Symptom Improvement

Figure 3 shows a comparison of the primary outcome measure (total symptom score) for the 3 groups at

Table 1. Patient Symptom and Quality of Life Scores Before Entering Into the Study

Symptom	Hypnotherapy	Supportive	Medical
Pain severity	5.6 (3.7–6.8)	5.7 (4.8–7.3)	5 (3.3–6.4)
Pain frequency	6 (4.6–7.1)	6.9 (5–8)	6 (4–7.4)
Nausea	1.6 (0–4.7)	4.1 (1.7–5.5)	2.4 (0–5.5)
Belching	5.4 (1.1–8)	5 (1–8.2)	3.4 (0.4–6.8)
Poor appetite	.8 (0–3.2)	2.3 (0–6)	2.3 (0–6)
Difficulty finishing meals	2.3 (0–5.4)	2.2 (0–6)	2.6 (0–5.7)
Bloatedness	4.7 (2–8)	7 (4–8.4)	5.1 (4–8)
Average total symptom score	3.5 (2.5–5.1)	4.2 (3.3–5.5)	3.7 (2.8–4.6)
QOL			
Psychic well-being	5.5 (4.4–7.1)	5.5 (4.5–7)	6.6 (5.6–7.7)
Physical well-being	4.3 (3.2–5)	4.8 (3.8–5.8)	5.3 (4.2–6.7)
Mood	3.7 (2.6–4.7)	3.6 (2.6–4.7)	4.5 (3.3–6.3)
Locus of control	6 (4.8–7.9)	6.2 (5.5–7.3)	7.6 (6–8.3)
Social relationships	6.9 (6–8)	6.9 (5.9–8.2)	7.6 (6.3–8.8)
Work/employment	5.9 (4.6–7)	6.5 (4.7–7.8)	6.8 (5.6–7.8)
Hobbies/interests	5 (3.5–6.3)	5 (3.5–7)	6 (5–7.5)
Finances	5.6 (3–8.1)	3.6 (2.4–5.4)	4.5 (2.4–8)
Average total QOL score	5.3 (4.6–6.1)	5.3 (4.2–6.5)	6.1 (5.4–7.3)

NOTE. Expressed as median (interquartile range).
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all time points during the course of the study. As can be seen, a highly significant improvement in symptoms occurred in the HT patients compared with the other 2 groups by the end of the short-term phase, and this was maintained during follow-up.

Short-Term. Figure 4 illustrates the percentage improvement in all symptoms at the end of the short-term phase. HT improved total symptom scores [percentage improvement, median (IQR) 59% (26%–85%)] more than either supportive [40.7% (10%–59%); $P = 0.057$] or medical [33% (−27% to −47.8%); $P = 0.01$] therapy. Significant differences favoring HT for the individual scores were also observed.

Long-term. At the end of the follow-up phase, patients receiving HT were significantly improved for the primary outcome measure [73% (26%–96%)] compared with either of the other 2 control groups [supportive, 34% (−24%–71%), $P < 0.02$; medical, 43% (15%–57%), $P < 0.01$]. In addition, all of the individual symptoms with the sole exception of nausea remained significantly improved following HT compared with the other 2 groups.

Quality of Life Improvement

Figure 5 shows a comparison of the total QOL scores for the 3 groups at all time points during the course of the study. QOL significantly improved in the HT group compared with the other 2 groups in the short-term. However, in the long-term, although HT significantly improved QOL compared with medical treatment, the supportive group did exhibit a slow improvement over time. A likely explanation for the unexpected improvement in QOL in the supportive group was that 5 patients in this group (compared with none in the other control group) began taking antidepressants during the follow-up phase, as shown in Table 3, which led to an improvement of this parameter.

Short-term. Figure 6 illustrates the percentage improvement in all components of QOL at the end of the short-term phase. As can be seen, this was significantly

Table 2. Scores for Total Symptoms and Quality of Life at Baseline and the End of the Short- and Long-Term Phases

	Baseline		Short-term (end of treatment)		Long-term (end of follow-up)	
	Total symptoms	Total quality of life	Total symptoms	Total quality of life	Total symptoms	Total quality of life
Hypnotherapy	3.5 (2.5–5.1)	5.3 (4.6–6.1)	1.1 (0.4–2.1)	7.9 (7–9.1)	.6 (.1–1.5)	8.6 (6.7–9.1)
Supportive	4.2 (3.3–3.5)	5.3 (4.2–6.5)	3.1 (2.2–4.6)	6.4 (5–7.5)	3.6 (1.5–5.2)	6.9 (6.2–8.1)
Medical	3.7 (2.8–4.6)	6.1 (5.4–7.3)	3 (1.1–4.3)	6.3 (4.9–7.9)	2.9 (1.4–3.7)	7.7 (6.9–8.1)

NOTE. Expressed as median (interquartile range). Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

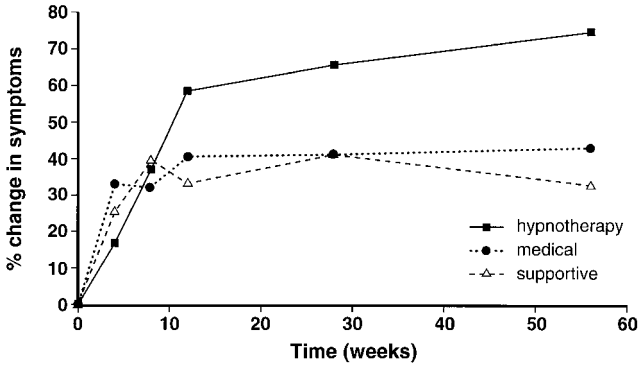

Figure 3. Symptom change throughout the study. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

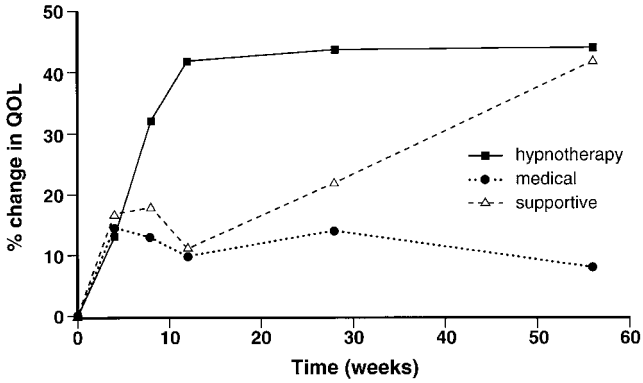

Figure 5. QOL change throughout the study. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

improved by HT [42% (31%–69%)] compared with both the medical [11% (−9%–46.6%) $P < 0.001$] and supportive [10% (−10%–21.2%); $P < 0.001$] groups. Significant differences favoring HT for the individual scores were also observed.

Long-term. At the end of the follow-up phase, QOL improved significantly with HT [44% (24%–69%)] compared with the medical [20% (10%–26%); $P < 0.01$] but not with the supportive group [43% (9%–60%)], for reasons already explained.

Dropouts

There were no significant differences between the initial symptom and QOL scores in any of the treatment groups for those patients who completed the treatment phase [total symptom score: HT, 3.3 (2.3–5.1); supportive, 4.4 (3.4–5.9); medical, 3.8 (2.9–5); total QOL score: HT, 5.3 (4.6–6.1); supportive, 5.3 (4.2–6.9); medical, 6.1 (5.4–7.3)] compared with those who dropped out [total symptom score: HT, 3.9 (3–5.4); supportive, 3.6 (2.8–4.7); medical, 3.6 (2.5–4.5); total QOL score: HT, 5.1 (4.6–6.5); supportive, 5.1 (4.7–5.8); medical, 5.8 (5.1–6.6)].

HAD Scores

The initial median HAD (anxiety) scores were at the upper limits of the normal range (score ≤9 is normal), whereas those for depression were well within normal limits (score ≤9 is normal). Patients in both the HT and supportive groups experienced a significant reduction in anxiety during the treatment phase of the study (anxiety score expressed as median [IQR]: HT pre, 8.5 [4.5–11.5], post, 5 [4.5–7], $P = 0.03$; supportive pre, 10 [8–11], post, 7 [4–9], $P = 0.02$). Anxiety was not significantly changed after medical treatment (pre, 8 [3.3–10.8]; post, 6.5 [4–9]). However, there were no significant differences in anxiety reduction during the treatment phase between the 3 groups.

Economic Factors

Table 3 provides data on medication use and consultation behavior during the 40-week follow-up

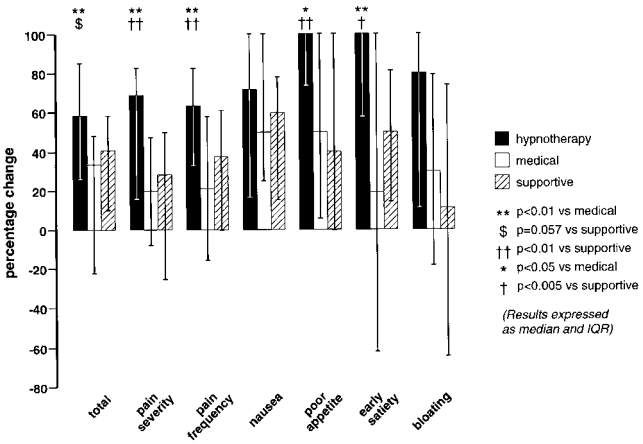

Figure 4. Symptom change during the short-term phase. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

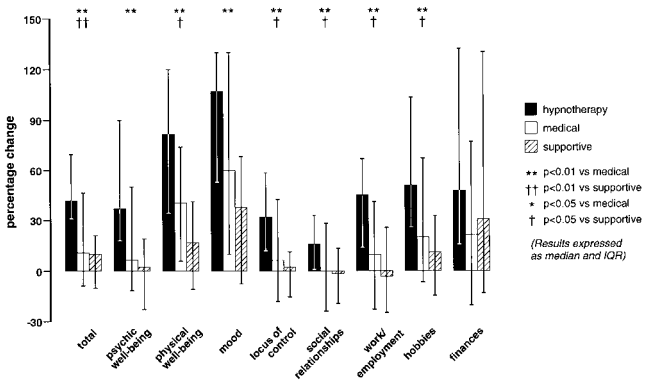

Figure 6. QOL change during the short-term phase. Reprinted with permission from Department of Medical Illustration, Withington Hospital, Manchester, England.

Table 3. Medication Use and Consultation Rate of Patients During the Long-term Follow-Up

	40-week follow-up		
	Hypnotherapy (n = 26)	Supportive (n = 24)	Medical (n = 29)
Number taking medication	0	20	26
% taking medication	0	81.8	89.7
PPI	0	6	15
H2 antagonists	0	8	8
Prokinetics	0	0	0
Antacids	0	4	3
Antidepressants	0	5	0
None	26	4	3
Total number of consultations median (IQR)	1 (0–2)	4 (1–10)*	4 (0–9)*
Number of GI consultations median (IQR)	0 (0–0)	3.5 (0–10)*	3 (0–9)*

NOTE. Expressed as median (interquartile range).
*$P < .001$ vs. hypnotherapy.
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phase. As can be seen, 82% of patients in the supportive group and 90% of patients in the medical group resorted to some form of medication, compared with 0 in the HT group ($P < 0.001$ HT vs. medical and supportive). The number of general practitioner or physician consultations was also significantly lower after HT than after either medical or supportive treatment during follow-up.

Discussion

This study clearly demonstrates that HT is more effective than medical treatment or supportive therapy plus placebo medication in both the short- and long-term management of FD. HT not only improves all aspects of symptomatology and QOL, but also has considerable economic advantages. Of particular interest is the striking difference in the medication needs of the 3 groups. None of the patients receiving HT resumed any form of drug therapy, whereas 90% of patients in the medical group and 82% of patients in the supportive group felt it necessary to begin some form of treatment. Five patients who received supportive therapy also began taking antidepressants during follow-up; this contributed to the somewhat surprising improvement in QOL observed in this group. A standard course of HT requires up to 12 sessions and thus at face value appears rather expensive in the short-term. However, this fails to take into account the fact that once treated, a patient seldom needs any further intervention—in sharp contrast to the conventional treatment of FD, in which expensive drugs (e.g., proton pump inhibitors) are often used on a long-term basis, even though they are of questionable efficacy. Furthermore, medically treated patients continue to consult much more than those managed with HT.

Interestingly, there were significantly more dropouts due to treatment failure in the 2 control groups than in the HT group ($P < 0.001$). The symptom severity of the dropouts was no worse than those remaining in the trial, suggesting that these were true treatment failures rather than being more severe. For HT to be an economically feasible treatment of any condition, it must be effective in the long-term without the need for continuing sessions, irrespective of any short-term gains. Thus it was essential that sufficient patients be recruited to each arm for the follow-up phase of the study; this was achieved by replacing dropouts. This policy inevitably resulted in recruitment of patients more likely to respond to control therapies and therefore biased the trial against HT for both the long- and short-term phases. Thus the results achieved for HT are even more encouraging.

There is a strong need for good quality-controlled trials in the area of "complementary" therapy (although some claim that these are impossible to undertake). Identifying suitable comparator groups presents some problems, and we felt it appropriate to have 2 control arms. The medical group provided an estimate of the standard response rate to medical treatment. The supportive group controlled for the time spent with the patient during HT, the necessity for which was confirmed by the reduced anxiety levels in the 2 groups receiving more attention. Those receiving supportive treatment were also given a placebo tablet, which served 3 functions: (1) to control for medication given to the medically treated group, (2) to maximize response to treatment to the greatest extent possible, and (3) as a result of needing further supplies of medication at each visit, ensuring they returned for sessions.

The mode of action of HT remains speculative but probably involves a number of different factors. There is undoubtedly a positive response to the increased attention, but this should have been adequately controlled for by the inclusion of a group receiving supportive therapy. Moreover, it is likely that the general relaxation associated with hypnosis provides a nonspecific psychotherapeutic response reducing anxiety. However, it should be noted that although anxiety declined during HT, there was no correlation with symptom improvement ($r = 0.220$, $P = 0.185$), suggesting that the beneficial effect cannot be attributed to anxiety reduction alone. The observation that HT can influence gastrointestinal physiologic function[17,18] might suggest that the improvement observed in FD may result from some modification

of gastric motility, gastric accommodation, or visceral sensitivity. It is of interest that although HT has been shown to modify gastric acid secretion,[15] its effects on other parameters of gastric physiology have not yet been assessed, although studies of this nature are now underway in our laboratory.

These results, taken in conjunction with those obtained for IBS,[10,11–14,24,25] confirm the efficacy of HT in a group of functional disorders that are especially difficult to treat. They also warrant the evaluation of this form of treatment in other functional problems not necessarily confined to the gastrointestinal tract.

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