Gut feelings: visceral hypersensitivity and functional gastrointestinal disorders
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CHAPTER 8
THE SELECTIVE SEROTONIN REUPTAKE INHIBITOR FLUOXETINE DOES NOT CHANGE RECTAL SENSITIVITY AND SYMPTOMS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME:
A DOUBLE BLIND, RANDOMISED, PLACEBO CONTROLLED STUDY

Sjoerd Kuiken, Guido Tytgat & Guy Boeckxstaens

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ABSTRACT

BACKGROUND & AIMS: Although widely prescribed, the evidence for the use of antidepressants for the treatment of the irritable bowel syndrome (IBS) is limited. In this study, we hypothesised that fluoxetine (Prozac®), a selective serotonin reuptake inhibitor, has visceral analgesic properties, leading to increased sensory thresholds during rectal distension and improvement of symptoms, in particular in IBS patients with visceral hypersensitivity.

METHODS: Forty non-depressed IBS patients underwent a rectal barostat study to assess the sensitivity to rectal distension before and after six weeks of treatment with fluoxetine 20 mg or placebo. Abdominal pain scores, individual gastrointestinal symptoms (GSRS), global symptom relief and psychological symptoms (SCL-90) were assessed before and after the intervention.

RESULTS: At baseline, 21/40 patients showed hypersensitivity to rectal distension. Fluoxetine did not significantly alter the threshold for discomfort / pain relative to placebo, neither in hypersensitive (19 ± 3 vs. 22 ± 2 mm Hg above MDP) nor in normosensitive (34 ± 2 vs. 39 ± 4 mm Hg above MDP) IBS patients. Overall, 53% of fluoxetine treated patients and 76% of placebo treated patients reported significant abdominal pain scores after six weeks (N.S). In contrast, in hypersensitive patients only, fluoxetine significantly reduced the number of patients reporting significant abdominal pain. Gastrointestinal symptoms, global symptom relief and psychological symptoms were not altered.

CONCLUSIONS: Fluoxetine does not change rectal sensitivity in IBS patients. Possible beneficial effects on pain perception need to be confirmed in larger trials.

ABBREVIATIONS: IBS: Irritable bowel syndrome; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; MDP: minimal distending pressure; HV: healthy volunteers
INTRODUCTION

The potential role of antidepressants in the treatment of the irritable bowel syndrome (IBS) is increasingly recognised, in particular for the treatment of abdominal pain associated with IBS. A recent meta-analysis of eleven published, randomised placebo controlled trials on the effectiveness of antidepressants in functional gastrointestinal disorders, of whom nine included IBS patients, showed a favourable outcome for both general symptom relief and pain scores during treatment with antidepressants. However, this analysis also revealed that the overall quality of the studies was low to moderate, mostly because of the limitations of blinding the study because of side effects. In addition, studies evaluating the efficacy of selective serotonin reuptake inhibitors (SSRIs) in IBS were not included, simply because these studies were not available. SSRIs have a favourable safety profile and better tolerability compared with tricyclic antidepressants (TCAs), and are therefore widely recommended in various guidelines and reviews on the treatment of IBS, despite the lack of objective clinical evidence. More recently, it was shown that the SSRI paroxetine improved health related quality of life in patients with IBS, compared with 'treatment as usual', further supporting a case for SSRIs in IBS, although placebo controlled studies are still awaited.

Thus, although the evidence is not fully conclusive, antidepressants seem effective in the treatment of IBS. However, the mechanisms by which antidepressants exert their action are still unclear. For example, although most, but certainly not all of the studies mentioned above assessed psychological symptoms, only two excluded patients with overt depression. Psychological symptoms, such as depression and anxiety are common in IBS patients. Therefore, the observed beneficial effects may also be explained by the psychotropic effects of the agents studied. In addition, no biological markers were used to assess the possible visceral analgesic properties of antidepressants in IBS, such as measurement of colorectal sensitivity. Further studies addressing these issues may not only improve the currently disappointing efficacy in the treatment of IBS symptoms, but also our understanding of the pathogenesis of IBS.

At present, enhanced visceral sensitivity or visceral hypersensitivity is regarded as a central mechanism in the development of IBS symptoms. Several promising new treatments with drugs shown to reduce visceral perception have recently come to attention, including the K-opioid receptor agonist fedotozine, the somatostatin analogue octreotide and the α2-adrenergic agonist clonidine. Antidepressants have neuromodulatory and analgesic properties, and there is evidence that antidepressants may also improve IBS symptoms by reducing visceral sensitivity. For example, the TCA amitriptyline increased the threshold for pain during rectal distension in patients with IBS, which correlated with symptom improvement. Notably, the visceral antinociceptive effect of antidepressants may be specific for states of visceral hypersensitivity, since amitriptyline did not alter visceral perception in healthy volunteers. This in contrast with studies on somatic pain, in which TCAs, but also other classes of antidepressants such as SSRIs, reduce the
Chapter 8

perception of pain in both healthy controls and in patients with various pain syndromes. In the present study, we hypothesised that fluoxetine, a well known SSRI, has visceral analgesic effects, leading to an increase in sensory thresholds during rectal distension. We anticipated that this effect would be more pronounced in patients with lowered sensory thresholds, or visceral hypersensitivity, compared with patients with normal rectal sensitivity. Therefore, we studied the effect of six weeks treatment with fluoxetine or placebo on rectal sensitivity in 40 consecutive, non-depressed IBS patients. As secondary endpoint, we also evaluated the effect of fluoxetine on IBS symptoms.

PATIENTS AND METHODS

STUDY SUBJECTS
Forty patients with irritable bowel syndrome (18 men and 22 women; age 18-59 years; mean age 40 ± 2 years) participated in the study. Based on their clinical history, 16/40 (40%) patients were considered as having diarrhoea predominant, 11/40 (28%) constipation predominant and 13/40 (32%) alternating type IBS. The mean duration of symptoms at intake was 5.9 ± 1 years (range 0.3-27 years). All patients had been unsuccessfully treated previously, of whom 32 (80%) had received bulking agents, 24 (60%) analgesics, 20 (50%) mebeverine, 6 (15%) cisapride and 5 (13%) osmotic laxatives. Only one patient had previously been treated unsuccessfully with an antidepressant (amitriptyline). In addition, in order to obtain normal values, 12 healthy volunteers (9 men and 3 women; age 19-60 years; mean age 40 ± 5 years) were studied. All healthy volunteers were free of gastrointestinal symptoms, without previous gastrointestinal surgery and not taking any medication.

The patients were recruited between February 1999 and September 2001 from the outpatients clinic of the departments of Gastroenterology and Internal Medicine at the Academic Medical Centre (AMC), a tertiary referral centre. Patients of 18 years and older with symptoms that fulfilled the Rome I criteria for irritable bowel syndrome were eligible to enter the study. A minimum work-up to exclude organic disease required normal physical examination, negative sigmoidoscopy / colonoscopy or barium contrast X-ray, normal thyroid stimulating hormone levels and blood counts and negative stool examinations. Patients had to be free of any concomitant disease, including psychiatric disorders. Before inclusion, patients filled out the Zung Self-rating Depression Scale (Zung SDS). This validated questionnaire contains 20 multiple choice items, with a score from 1 to 4 each, so that the total raw point score can range from 20 to 80. Raw scores of more than 49 are considered high and indicative for depression. Therefore, only patients with a raw score of < 50 were included. In our population, the mean Zung SDS score was 38 ± 1 (range 23-48).

Concomitant medication likely to interfere with gastrointestinal tract function or
visceral perception other than fibres or bulking agents was discontinued before entering the study. Patients were excluded if they were pregnant, breast-feeding or of childbearing potential and not using appropriate methods of contraception. Patients who underwent previous abdominal surgery, except for uncomplicated appendectomy, were also excluded. All participants gave their written and informed consent to participate in the study. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Centre.

STUDY DESIGN
Both healthy volunteers and patients with IBS were invited to participate. 12 healthy volunteers devoid of any gastrointestinal symptoms underwent the same barostat protocol as the IBS patients. These data were used to determine normal perceptive thresholds by which patients with rectal hypersensitivity could be identified.

Patients fulfilling the Rome I criteria were first asked to fill out the Zung SDS. Only after exclusion of a clinical significant depression, patients were further eligible to participate. In addition, all patients filled out three different questionnaires (see below) to assess their IBS symptoms and psychological symptoms. Thereafter, a rectal barostat study was performed to assess the sensitivity to rectal distension. Subsequently, patients were randomised 1:1 to receive six weeks oral treatment with equal capsules containing either placebo or fluoxetine 20 mg once daily at bed time, in a double blind fashion. Treatments were randomly assigned by the local hospital pharmacy using a randomisation schedule generated by a standardised computer program (Random, dept. of Biostatistics AMC Amsterdam, the Netherlands). Fluoxetine (Prozac®) was supplied by Eli Lilly and Company, Houten, the Netherlands. IBS symptoms and psychological symptoms were scored after two and six weeks treatment. In addition, patients were asked if they experienced global symptom relief (see below). After six weeks, a second rectal barostat study was performed to assess changes in rectal sensitivity. There was no follow-up period included in the protocol.

BAROSTAT STUDIES
To assess the sensitivity to rectal distension, we used an electronic barostat that automatically corrected for the compressibility of air (Synetics Visceral Stimulator, Stockholm, Sweden). Before the distension studies, subjects received a tap water enema. Sixty minutes thereafter, a 500-ml polyethylene bag (maximal diameter 9 cm), tightly wrapped on the distal end of a double lumen polyvinyl tube (Salem Sump tube 14 Ch.; Sherwood Medical St Louis, USA) was introduced in the rectum using a plastic overtube. The catheter was then connected to the barostat device and the subject was placed in the left lateral decubitus position. The bag was unfolded by inflating it with 200 ml of air and positioned in the distal rectum by gently pulling the catheter back. After a 15-minute adaptation period, minimal distending pressure (MDP) was determined as the minimum pressure at which the intrabag volume was >30 ml. This pressure level equals the intra-abdominal pressure. Subsequently, a series of phasic, semirandomly ascending isobaric
destinations was performed (phasic distension), followed by a second distension at a constant inflation rate (volume ramp distension), separated by a 15-min recuperation period with the bag deflated. During both distension series, subjects scored the perception of sensations evoked by rectal distension using a 6-point scale with verbal descriptors (0= no sensation; 1= first sensation; 2= first urge to defecate; 3= normal urge to defecate; 4= severe urge to defecate; 5= discomfort / pain). Sensation scores were automatically logged onto the data file at each score point.

**Phasic distension:** The first distension series was performed using a phasic, semirandomly ascending isobaric protocol of 3 mm Hg increment above MDP (3, 6, 12, 9, 18, 15, 24, 21, 30 mm Hg, etc.), at 38 ml/s, of 2 minutes duration and separated by 1-minute intervals at baseline (MDP). Sensations were scored halfway (at 1 minute) each distension step. The bag was instantaneously deflated if the subject reported discomfort or pain. For safety, the bag was automatically deflated at pressures above 60 mm Hg or volumes above 500 ml. Corresponding volumes during phasic distension were recorded continuously.

**Volume ramp distension:** 15 min after the phasic distension series, a second distension was performed at a constant inflation rate of 40 ml/min, starting at 0 ml. Subjects reported when they first perceived sensations corresponding with 1, 2, 3, 4 and 5 on the scale mentioned above. Again, the bag was deflated if the subject reported discomfort or if the maximum intrabag volume (>500 ml) or pressure (>60 mm Hg) was reached. Corresponding pressures during ramp distension were recorded continuously.

**SYMPTOM ASSESSMENT**

**Abdominal pain scores:** We used a 5-point score to assess the severity of abdominal pain. Patients had to answer the following question: 'please consider how much abdominal pain you experienced in the past 4 weeks'. Possible answers were: 1= None; 2= Mild; 3= Moderate; 4= Severe; 5= Very Severe.

**Gastrointestinal symptoms:** The severity of IBS symptoms of abdominal bloating, flatulence, urgency and the feeling of incomplete evacuation was scored before, at two weeks and after six weeks treatment, on a self-rated scale, derived from the validated Gastrointestinal Symptom Rating Scale (GSRS), in which symptoms are rated on a 7-graded Likert scale, with descriptive anchors ranging from 'no discomfort at all' (=0) to 'very severe discomfort' (=6)\textsuperscript{20}.

**Global symptom relief:** Global symptom relief was assessed after two and six weeks treatment by answering the following question: 'Please consider how you felt the past two weeks in regard to your irritable bowel syndrome. Compared to the way you felt before entering the study, how would you rate your relief of symptoms during the past two weeks?' Possible answers were: relieved; unchanged; or worse.
Psychological symptoms: Psychological symptom scores were obtained using the validated Symptoms Check List 90 (SCL-90)\textsuperscript{21}. The SCL-90 is a self rated questionnaire, consisting of 90 items, designed to assess various dimensions of psychopathology. These include interpersonal sensitivity (including distrust), hostility, depression, anxiety, agoraphobia, insufficiency of functioning (obsessive-compulsive behaviour) and sleep disturbance. Population norms were available from studies carried out in the Netherlands\textsuperscript{22}.

DATA ANALYSIS
Primary endpoints were the thresholds for discomfort / pain during rectal distension. Secondary endpoints were abdominal pain scores and individual gastrointestinal symptoms, global symptom relieve and psychological symptoms.

Thresholds for first sensation, urge and discomfort / pain during both phasic and volume ramp distension were assessed before and after the intervention period. Since hypersensitivity is best elicited by rapid, phasic distension protocols\textsuperscript{23}, we used the threshold for discomfort / pain obtained during phasic distension to determine hypersensitivity to rectal distension. Hypersensitivity was defined as a threshold for discomfort / pain during phasic distension of less than the 10\textsuperscript{th} percentile of healthy volunteers. Rectal compliance was calculated as the slope of the pressure-volume curve during phasic distension, obtained by measuring the mean intrabag volumes over the last 60 s of each distension step and plotting it against the corresponding distending pressure. Gastrointestinal symptoms (GSRS) and abdominal pain scores were considered significant if patients reported a score of at least 4, on a scale of 0-6 and 1-5 respectively. The proportion of patients who reported global relieve of IBS symptoms was assessed after 2 and six weeks treatment. SCL-90 scores were obtained before and after the intervention period and compared within and between groups. In addition, the number of patients with abnormal SCL-90 subscores compared to the national normative value was assessed.

STATISTICS
The primary endpoint was the threshold for discomfort / pain during rectal distension. Based on data derived from a previous study, showing that octreotide significantly increased the pain threshold in IBS patients\textsuperscript{10}, we assumed that the common standard deviation would be 6 mm Hg, and that a relevant detectable difference would be 8.4 mm Hg, (standardised difference = 1.4). This would require 10 patients in each treatment group in order to obtain a power of 90\% at the 5\% one-sided significance level. As we wanted to compare normosensitive and hypersensitive patients and approximately 50\% of IBS patients exhibit hypersensitivity to rectal distension, 20 patients were included in each treatment group. In addition, this number would give sufficient statistical power (i.e. at least 85\% power at the 5\% significance level) to detect differences in symptom scores of \textgeq1 SD between treatments within the overall group. Continuous data were compared using the Student t-test for independent samples and the paired t-test for related samples. Nominal data were compared by the Mann-Whitney U test (independent samples) or the Wilcoxon signed rank test (related samples).
Comparison of proportions was performed using Chi-square testing, with Fisher's correction when appropriate. Differences were considered significant at the 5% level. Data are presented as mean ± SEM for continuous data and median (interquartile range) for nominal data. Statistical evaluations were performed using commercially available software (SPSS 11.0; SPSS Inc. Chicago IL, USA).

RESULTS

RECTAL SENSITIVITY IN IBS: COMPARISON WITH HEALTHY VOLUNTEERS

Healthy volunteers

Pressure sensitivity: In healthy volunteers (HV), MDP was 6 ± 1 mm Hg. Thresholds for first sensation, urge and discomfort / pain during phasic, isobaric distension were 6 ± 1, 14 ± 2 and 39 ± 3 mm Hg above MDP respectively (Table 1). The lower limit of normal for discomfort / pain, defined as the 10th percentile of the threshold for discomfort / pain in healthy volunteers, was 25 mm Hg (Figure 1).

Volume sensitivity: During volume ramp distension, thresholds for first sensation, urge and discomfort / pain were 105 ± 33, 232 ± 33 and 348 ± 27 ml respectively.

Rectal compliance: The slope of the pressure-volume curve was calculated from the data obtained during phasic distension. In HV, the slope of the pressure-volume curve was 6 ± 1 ml / mm Hg.

IBS patients at baseline

Pressure sensitivity: In IBS patients, MDP was 8 ± 1 mm Hg, and thresholds for first sensation and urge during phasic distension were 4 ± 1 and 12 ± 1 above MDP respectively (not significantly different from HV; See Table 1). In contrast, the threshold for discomfort was significantly decreased compared with HV (29 ± 2 vs. 39 ± 3 mm Hg above MDP, P= 0.01). Using the 10th percentile of HV as the lower limit of normal (≥ 25 mm Hg), 21 patients (53%) had a decreased threshold for discomfort / pain during phasic, isobaric distension, and were therefore considered hypersensitive to rectal distension (Figure 1). Patients characterised by hypersensitivity to rectal distension had significantly lower thresholds for first sensation, urge and discomfort during phasic distension, compared with HV, whereas patients with normal sensitivity had sensory thresholds comparable with HV (See Table 1).
Fluoxetine & IBS

<table>
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**Table 1:** Perceptive thresholds (mm Hg above MDP) during phasic, isobaric distension. Values are means ± SEM. *P < 0.05 versus healthy volunteers

**Figure 1.** Individual thresholds (mm Hg above MDP) for discomfort / pain during phasic, isobaric rectal distension in 12 healthy volunteers (HV) and 40 IBS patients (IBS) with no active treatment (before intervention). Using the 10th percentile of HV as the lower limit of normal (≥ 25 mm Hg), 21 patients (53%) had a decreased threshold for discomfort / pain, and were therefore considered hypersensitive to rectal distension.

**Volume sensitivity:** Thresholds for first sensation and urge during volume ramp distension were not significantly different for IBS patients, compared with HV (first sensation: 79 ± 11 vs. 105 ± 33 ml; urge: 186 ± 12 vs. 232 ± 33 ml), whereas the threshold for discomfort / pain was significantly decreased (279 ± 12 ml vs. 348 ± 26, P= 0.01). Patients characterised by hypersensitivity to *phasic* rectal distension...
Chapter 8

showed comparable thresholds for first sensation (74 ± 15 vs. 105 ± 33 ml), tended to report decreased thresholds for urge (164 ± 17 vs. 232 ± 33 ml, \( P=0.05 \)); and had significantly decreased thresholds for discomfort / pain (232 ± 33 vs. 348 ± 27 ml, \( P=0.002 \)) during volume ramp distension, compared with HV. In patients with normal sensitivity, sensory thresholds were comparable with HV (first sensation: 86 ± 14 vs. 105 ± 33 ml; urge: 214 ± 13 vs. 232 ± 33 ml; and discomfort / pain 317 ± 17 vs. 348 ± 27 ml).

Rectal compliance: The slope of the pressure-volume curve in IBS patients (phasic distension) was 7 ± 1 ml / mm Hg (not significantly different from HV), which was similar for hypersensitive (8 ±1 ml / mm Hg) and normosensitive (6 ± 1 ml / mm Hg) patients.

EFFECTS OF FLUOXETINE IN IBS PATIENTS

Treatment, tolerability and side effects

Of the 40 patients that entered the study, 19 (12 female) were randomised to receive fluoxetine and 21 (10 female) placebo. The proportion of patients with hypersensitivity to rectal distension was not significantly different in the fluoxetine group compared with placebo (8/19 (42%) and 13/21 (62%) respectively). A total of 34 patients completed the study. Six dropped out because of intolerable side effects, 2 in the fluoxetine group (both normosensitive) and 4 in the placebo group (3 hypersensitive). Overall, the number of patients reporting side effects was comparable between the groups (placebo: 8 patients vs. fluoxetine: 10 patients). The most frequent complaints were dizziness and drowsiness, and less frequently diarrhea, constipation, headaches, nausea and itching.

Effect of fluoxetine on rectal sensitivity

Pressure sensitivity: At baseline, sensory thresholds during phasic, isobaric distension were not significantly different for patients who were randomised to receive fluoxetine, compared with those assigned to receive placebo (first sensation: 5 ± 1 and 4 ± 1 mm Hg, respectively; urge: 14 ± 2 and 11 ± 1 mm Hg, respectively; and discomfort / pain: 30 ± 3 and 28 ± 3 mm Hg, respectively, see Figure 2). After six weeks treatment, no changes in the thresholds for first sensation, urge and discomfort / pain were observed in the fluoxetine treated group, compared with placebo (first sensation: 5 ± 1 and 4 ± 1 mm Hg, respectively; urge: 14 ± 3 and 13 ± 2 mm Hg, respectively; discomfort / pain: 28 ± 3 and 29 ± 3 mm Hg, respectively, see Figure 2).
Figure 2. Effect of fluoxetine (hatched bars) and placebo (open bars) on the threshold (mm Hg above MDP) for discomfort / pain during phasic, isobaric rectal distension in IBS patients. Data are expressed as means ± SEM. No significant differences were observed.

Volume sensitivity: The sensory thresholds during volume ramp distension for patients in the fluoxetine group were not different from those of patients in the placebo group before the intervention (first sensation: 73 ± 15 and 84 ± 15 ml, respectively; urge: 182 ± 17 and 189 ± 17 ml, respectively; and discomfort / pain: 278 ± 19 and 279 ± 17 ml, respectively). After six weeks treatment, the thresholds for first sensation, urge and discomfort / pain were not significantly altered by fluoxetine, compared with placebo (first sensation: 93 ± 20 and 94 ± 15 ml, respectively; urge: 188 ± 20 and 215 ± 22 ml respectively; discomfort / pain: 281 ± 18 and 303 ± 22 ml respectively).

Rectal compliance: The slope of the pressure-volume curve obtained during phasic distension was comparable between the treatment groups before intervention (fluoxetine: 7 ± 1 vs. placebo: 8 ± 1 ml /mm Hg) and this was not significantly altered after six weeks (fluoxetine: 7 ± 1 vs. placebo: 8 ± 1 ml /mm Hg).

Effects of fluoxetine on symptoms
Abdominal pain: At baseline, before treatment, the proportion of patients reporting significant abdominal pain was not significantly different for patients randomised to receive fluoxetine or placebo (89% and 76% respectively). Although the proportion of patients reporting significant abdominal pain was significantly smaller after six weeks treatment with fluoxetine, compared to baseline (53% vs. 89 %, P= 0.03, see Figure 3), which was not seen in the placebo treated group (76% vs. 76 %), the difference between the treatment groups did not reach statistical significance at six weeks (fluoxetine: 53% vs. placebo: 76%, P= 0.2; see Figure 3).
Gastrointestinal symptoms: The proportion of patients reporting significant symptoms of bloating, flatulence, urgency and incomplete evacuation was also not significantly different at baseline for patients randomised to receive fluoxetine or placebo (bloating: 53% and 48%, respectively; flatulence: 58% and 56%, respectively; urgency: 32% and 33%, respectively; and incomplete evacuation: 53% and 43% respectively). After six weeks treatment with fluoxetine, no significant differences were observed, for any of the symptoms, compared with placebo (bloating: 59% and 47%, respectively; flatulence: 63% and 53%, respectively; urgency: 41% and 18%, respectively; and incomplete evacuation: 50% and 29% respectively). Symptom scores obtained after two weeks also showed no significant differences between the treatment groups for any of the symptom scores (data not shown).

Global symptom relief: After two weeks treatment, 16% of patients in de fluoxetine group reported global relief of their IBS symptoms, compared to 24% in the placebo group (not significant). Although more patients reported global relief after six weeks in both treatment groups, there was no significant difference between fluoxetine (53%) and placebo (43%).

Psychological symptoms: Psychological symptom scores were obtained using the SCL-90 check list. Compared to normal values, derived from the general population in the Netherlands, 7 (18%) patients had abnormal scores for sleep disturbance, 5 (13%) for insufficiency of functioning, 5 (13%) for somatisation 3 (8%) for agoraphobia, 2 (5%) for anxiety, 2 (5%) for depression, 1 (3%) for interpersonal sensitivity and 1 (3%) for hostility, as assessed before treatment (N=40). At baseline, the proportion of patients with abnormal SCL-90 subscores was not significantly different for patients randomised to receive fluoxetine or placebo. Table 2 summarises the median scores (interquartile range) of the individual SCL

![Abdominal pain](image)
subscores, before and after treatment with fluoxetine or placebo for the overall group of patients. Fluoxetine did not significantly alter any of the individual psychological symptom scores, compared with placebo.

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<td>Sleep disturbance</td>
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</table>

**TABLE 2. SCL-90 subscores for psychological symptoms. Values are medians (interquartile range). No significant differences were found.**

**HYPERSENSITIVE VERSUS NORMOSENSITIVE PATIENTS**

**Rectal sensitivity**

*Pressure sensitivity:* At baseline, both hypersensitive and normosensitive patients who were randomised to receive fluoxetine had comparable thresholds for discomfort/pain, compared with those assigned to receive placebo (hypersensitive: 18 ± 2 and 19 ± 1 mm Hg, respectively; normosensitive: 39 ± 3 and 39 ± 3 mm Hg, respectively). As we hypothesised that fluoxetine would reduce rectal sensitivity, we anticipated that this effect should preferentially be detected in hypersensitive patients. However, fluoxetine did not significantly alter the mean threshold for discomfort/pain compared with placebo, neither in hypersensitive (18 ± 2 versus 19 ± 1 mm Hg) nor in normosensitive (34 ± 2 versus 39 ± 4 mm Hg) patients. In addition, individual discomfort thresholds remained unaltered during both treatments, both in normosensitive and hypersensitive patients (see Figure 4).

*Volume sensitivity:* Maximum tolerable volume, or the threshold for discomfort/pain during volume ramp distension in the fluoxetine group was not significantly different from the placebo group both for hypersensitive (before: 241 ± 22 and 256 ± 21 ml respectively; after six weeks: 246 ± 24 and 279 ± 35 ml respectively) and normosensitive (before: 315 ± 26 and 319 ± 22 ml respectively; after six weeks: 311 ± 23 and 334 ± 18 ml respectively) patients.
Figure 4. Evolution of individual thresholds for discomfort/pain during rectal distension studies before and after 6 weeks treatment with placebo or fluoxetine. Normosensitive: Patients characterised by normal sensitivity; and Hypersensitive: Patients characterised by hypersensitivity to rectal distension.

Rectal compliance: The slope of the pressure-volume curve obtained during phasic distension was comparable between fluoxetine and placebo treated patients before intervention (hypersensitive patients: 8 ± 1 and 9 ± 1 ml / mm Hg, respectively; normosensitive patients: 7 ± 1 and 6 ± 1 ml / mm Hg, respectively), and this was not significantly altered after six weeks treatment (hypersensitive patients: 7 ± 1 and 9 ± 1 ml / mmHg, respectively; normosensitive patients: 7 ± 1 and 6 ± 1 ml / mmHg, respectively).

Symptoms
Although this study was powered to study a possible effect of fluoxetine on rectal sensitivity in both hypersensitive and normosensitive subjects and on symptoms for
the overall treated patients, we also performed *post-hoc* analysis of symptoms based on the presence of hypersensitivity. We did this because we wanted to generate clues for directing future studies on new treatments for IBS.

In general, symptom scores at baseline were comparable for hypersensitive and normosensitive patients, except for psychological symptom scores. That is, hypersensitive patients tended to report decreased SCL-90 scores compared with normosensitive patients, illustrated by significantly lower scores for depression (28 (24-31) vs. 22 (20-25) *P*=0.02), anxiety (15 (13-18) vs. 12 (10-15), *P*=0.04) and interpersonal sensitivity (27 (21-38) vs. 22 (18-23) *P*=0.04).

Symptoms of bloating, flatulence, urgency and incomplete evacuation and global symptom relief were not significantly altered by fluoxetine, compared with placebo if hypersensitive and normosensitive patients were analyzed separately. In contrast, the proportion of hypersensitive patients reporting significant abdominal pain was significantly lower after six weeks fluoxetine, compared with placebo (3/8 (38%) and 9/10 (90%), respectively, *P* = 0.04; see Figure 5), which was not seen in normosensitive patients (6/9 (67%) and 4/7 (57%), respectively, see Figure 5). There were no significant differences between hypersensitive and normosensitive patients in response to both treatments on psychiatric symptom scores.

**Figure 5.** Bars representing the proportion of patients reporting significant abdominal pain (i.e. minimal 4 on a 1-5 scale) before and after 6 weeks treatment with fluoxetine (hatched bars) and placebo (open bars). Separate analysis was performed in hypersensitive and normosensitive patients.

*P* <0.05 by Chi-square.

**DISCUSSION**

Our study demonstrates that fluoxetine has no effects on visceral sensitivity, questioning its visceral analgesic properties in non-depressed IBS patients. In addition, no effect on IBS symptoms could be demonstrated in the overall treated patients. However, in patients with hypersensitivity to rectal distension, fluoxetine reduced the number of patients reporting significant abdominal pain, which was not observed in patients with normal rectal sensitivity. Future, larger clinical trials are
certainly required to confirm this.

There is increasing evidence that antidepressants are effective in the treatment of patients with IBS. However, the objective clinical evidence is scarce, and mechanistic insights in how antidepressants could work in IBS are lacking. In addition to their psychotropic action, antidepressants have neuromodulatory and analgesic properties, of which the most convincing clinical evidence comes from experimental models of somatic pain and various somatic pain syndromes. These studies also confirm the analgesic potential of SSRI s (including fluoxetine), although TCAs, in particular amitriptyline, seem superior in this perspective and are certainly the best studied. The mechanisms by which antidepressants have analgesic effects are largely unknown, but seem to be independent from their psychotropic action. The modulation of nociceptive stimuli by antidepressants has been suggested to involve serotonergic, noradrenergic and opioidergic systems, and are most likely centrally mediated, although the involvement of spinal and / or peripheral mechanisms has not been well established. These findings have led to the evaluation of antidepressants in visceral sensitivity. Visceral hypersensitivity is considered one of the major pathophysiological mechanisms underlying the generation of symptoms in IBS and can be demonstrated as hypersensitivity to rectal distension in 20-80% of IBS patients across studies. From a therapeutic point of view, restoring normal visceral sensitivity would be a promising approach to treat patients with IBS. In previous studies, amitriptyline increased the threshold for pain during rectal distension in IBS patients, whereas imipramine, another TCA, reduced esophageal sensitivity in both healthy controls and in patients with noncardiac chest pain, suggesting that antidepressants may have visceral analgesic properties.

In this study however, the SSRI fluoxetine did not change the thresholds for discomfort / pain during phasic, isobaric rectal distension in IBS patients. Also, if patients with hypersensitivity were analysed separately, no effects on rectal sensitivity could be demonstrated. These findings argue against a visceral analgesic effect of fluoxetine. In addition, no effects on maximum tolerated volume or rectal wall compliance were observed, excluding an effect on rectal tone. Possible beneficial effects of fluoxetine in IBS patients can therefore not be explained by alterations in gut sensitivity and / or relaxation of the gut wall.

We could not demonstrate any overall effects of fluoxetine on IBS symptoms, compared with placebo. Theoretically, the possible prokinetic side effects SSRIs such as fluoxetine may be beneficial for the treatment of constipation related symptoms and gas retention in IBS subgroups. However, this needs to be further studied. At least in this population and with the current dose, we could not demonstrate any effects on symptoms of bloating, flatulence, urgency or the feeling of incomplete evacuation. The effects of fluoxetine on pain perception were less conclusive. Although no significant difference could be demonstrated between treatments for the overall treated patients, fluoxetine significantly decreased the proportion of patients reporting significant abdominal pain scores compared to baseline, which was not seen during treatment with placebo. In addition, hypersensitive, but not normosensitive patients reported less severe pain scores.
after 6 weeks fluoxetine, which was statistically significant compared with placebo. Although these data should be interpreted with caution because of the limited number of patients, this may have implications for future study designs further evaluating the antinociceptive effects of SSRIs in IBS, since patients characterised by visceral hypersensitivity may respond better to treatment. Whether this can be confirmed in larger studies and how this can be explained needs to be awaited.

To our knowledge, this is the first placebo controlled study evaluating the effect of a selective serotonin reuptake inhibitor (SSRI) on visceral perception and IBS symptoms. However, the use of SSRIs is widely recommended in various guidelines and reviews on the treatment of IBS.6-8 Besides unpublished clinical experience, these recommendations are based on one uncontrolled retrospective study and a few case reports. More recently, it was shown that the SSRI paroxetine increased health related quality of life in IBS, in a randomised comparative study with psychotherapy and routine treatment. It should be emphasised though that in addition to their uncontrolled nature, all of these studies included patients with documented concomitant clinical depression. In contrast, we included only non-depressed IBS patients. In addition, no effects on psychological symptoms could be demonstrated. Therefore, the observed beneficial effects of fluoxetine in clinical practice may depend mainly on its psychotropie action, possibly explaining the lack of effect on symptoms in our selection of patients. Whether this also applies to other types of antidepressants for IBS, such as TCAs, needs to be further clarified. For example, there is evidence that amitriptyline does indeed decrease rectal sensitivity in IBS patients, although this too was not a placebo controlled study. Given the limitations of our study, we can only speculate on these issues. However, as long as there are no mechanistic insights in how antidepressants work in IBS, we cannot rule out the possibility that it is treating concomitant psychiatric symptoms from which IBS patients benefit most.

We perceive that there are several limitations in the interpretation of this study. Firstly, the number of patients studied is rather limited to exclude any effects on symptom relief. We powered our study based on the primary end-point, i.e. the threshold for pain / discomfort during rectal distension. In case a phase II trial was to be performed based on symptom improvement, we would need a substantial larger sample size. For example, if we took global symptom relief as endpoint for future studies, a sample size of 426 in each group would be needed to confirm a 10% point difference with a placebo response of as high as 43 %, as found in the current study. Such small differences with placebo are rather usual in IBS as seen in recent successful trials with promising agents such as 5-HT agonists and antagonists, reporting percentage point differences of 11 to 17. Thus, our data should be interpreted with caution with respect to the overall benefits of fluoxetine for IBS patients. Secondly, our method of assessing visceral sensitivity using rectal balloon distension may not be the method of choice to detect subtle changes in visceral sensitivity. One disadvantage of our approach could be that in general, protocols requiring repetitive stimuli are time consuming and therefore subject to elements of fatigue or perceptual bias. However, we aimed to limit this anticipatory behaviour by delivering the various distensions in a pseudo-random
order, as described previously. Alternatively, changes in visceral sensitivity in IBS may be more pronounced if assessed by distending the colon or even the small bowel. However, at present, there are no clear data showing which method of testing visceral sensitivity is more sensitive and thus should be the method of choice for assessing possible visceral analgesic agents in IBS patients. Finally, although we applied the Rome I criteria instead of the revised and more stringent Rome II criteria, patients were recruited from a tertiary referral centre, and may therefore represent a more seriously affected population of patients, so that the results of this study may not be applicable to the average IBS patient.

In conclusion, fluoxetine does not change rectal sensitivity and symptoms in IBS patients. Therefore, the beneficial effects of fluoxetine for IBS seem limited. Further objective studies are needed to verify the proposed role of SSRIs in the treatment of IBS symptoms. These studies need to further clarify important issues such as the impact of possible concomitant psychiatric disease, different subclasses and different doses of SSRIs, comparison with other classes of antidepressant agents such as TCAs, and possible differential effects for visceral hypersensitive and normosensitive patients.

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