

# Selective serotonin reuptake inhibitors for the management of irritable bowel syndrome: A meta-analysis of randomized controlled trials

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## Abstract

**Introduction:** Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs used for the management of irritable bowel syndrome (IBS) but there is not enough evidence to prove their effectiveness. The aim of the study was to evaluate the efficacy of SSRIs for the management of IBS by meta-analysis technique.

**Material and methods:** PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies that investigated efficacy of SSRIs in the management of IBS. Search terms used were “fluoxetine”, “sertraline”, “paroxetine”, “citalopram”, “escitalopram”, or “fluvoxamine” and “irritable bowel”, “functional bowel diseases” or “irritable colon”. Data were searched within the period of 1966 to September 2007. Controlled trials investigating the efficacy of SSRIs in patients with IBS were considered.

**Results:** Five randomized placebo controlled clinical trials met our criteria and were included in the meta-analysis. Pooling of 4 trials for the outcome of improvement in abdominal pain yielded a non-significant odds ratio of 4.68 (95% confidence interval CI of 0.64-34.26,  $p < 0.1268$ ). Pooling 3 studies, from which data for improvement of abdominal bloating were extracted, yielded a non-significant odds ratio of 2.46 (95% CI of 0.4-15.17,  $p < 0.33141$ ). The summary odds ratio for relief of IBS symptoms outcomes among SSRI therapy in 2 trials was 1.31 (95% CI of 0.5-3.39,  $p < 0.5848$ ), a non-significant OR.

**Conclusions:** SSRIs do not significantly improve abdominal pain, abdominal bloating and IBS symptoms. The present results indicate that despite a statistically non-significant effect of SSRIs intake on improving abdominal pain in IBS patients, there is a 5-fold improvement in pain control.

**Key words:** meta-analysis, selective serotonin reuptake inhibitors, irritable bowel syndrome, efficacy.

## Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder characterized by abdominal pain or discomfort and alterations in bowel habits [1]. There are different reports about the prevalence of IBS. It affects up to 20% of the North American population [2]. A study carried out in Birmingham reports that the community-based prevalence of IBS is 10.5% [3]. IBS is seen in women almost two times more than men [3, 4]. Environmental factors (psychological disturbances and stress), genetic

links, previous infection, small intestinal bacterial overgrowth, food intolerance, altered bowel motility and/or secretion, visceral hypersensitivity, altered central nervous system sensory processing, disturbed autonomic nervous system regulation, and serotonin dysregulation are known as possible aetiological factors for IBS [1, 5]. It has been suggested that selective serotonin reuptake inhibitors (SSRIs) may be useful for the management of IBS. SSRIs are a class of antidepressants used in the treatment of depression, anxiety disorders, and some personality disorders. Although the exact mechanisms by which SSRIs may be useful in the management of IBS are not fully understood, since psychological stressors play an important role in the pathophysiology of IBS it seems that SSRIs may show benefits for IBS by their antidepressant action. The clinical trials that evaluated the efficacy of SSRIs in the management of IBS have reported conflicting results; after administration of citalopram to 15 IBS patients in an open-label pilot study, 80% of the subjects reported a significant decrease in the presence of abdominal pain, 67% reported a significant reduction in the severity of the symptom, and 80% reported a considerable reduction in the frequency of the symptom [6]. In another open-label pilot study on 20 IBS patients treated with paroxetine, 65% reported a reduction in abdominal pain, and 55% reported a reduction in pain frequency. Constipation and diarrhoea were reduced in 69 and 57% of patients, respectively. Similarly, a clinically significant reduction in the symptoms of feeling of incomplete emptying was apparent. At week 12, 47% of the patients were much or very much improved [7]. In two case reports, IBS symptoms disappeared in 2 patients with a history of stress in their life after exposure to paroxetine for 3 weeks [8, 9]. A marked decrease in symptoms of urgency, stomach cramps, loose stools, and constipation occurred in a patient with IBS after prescription of fluvoxamine [10]. Use of paroxetine in IBS improved overall well-being as compared to a placebo group but no significant difference in abdominal pain, bloating or social functioning was shown between the paroxetine and placebo groups [11]. After 6 weeks' administration of fluoxetine to IBS patients, a significant reduction in abdominal pain was reported. GI symptoms, global symptom relief, and psychological symptoms were not altered [12]. Citalopram significantly improved abdominal pain, bloating, impact of symptoms on daily life, and overall well being as compared to placebo after 6 weeks of treatment [13]. There was no significant difference between citalopram and placebo in adequate relief of IBS symptoms [14]. Fluoxetine was significantly more effective than placebo in decreasing abdominal discomfort, relieving feeling

and sense of bloating, increasing frequency of bowel movements and decreasing consistency of stool in patients with pain and constipation-predominant IBS [15]. Since there is no meta-analyses on the efficacy of SSRIs in IBS, we aimed to perform the present meta-analysis by evaluating all randomized controlled trials to reach a better conclusion about the efficacy of this class of drugs for treatment of IBS.

## Material and methods

### Data sources

PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies that investigated efficacy of SSRIs in IBS. Data were collected from 1966 to 2007 (up to September). The search terms were: "fluoxetine", "sertraline", "paroxetine", "citalopram", "escitalopram", or "fluvoxamine" and "irritable bowel", "functional bowel diseases" or "irritable colon". There was no language restriction. The reference list from retrieved articles was also reviewed for additional applicable studies.

### Study selection

Controlled trials investigating the efficacy of SSRIs in patients with IBS were considered. "Improvement of abdominal pain", "improvement of abdominal bloating" and "improvement of IBS symptoms" were considered as the key outcomes. We evaluated all published studies as well as abstracts presented at meetings. Three reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies, and uncontrolled trials. Trials were disqualified if they compared SSRIs with other drugs instead of placebo or they did not investigate the considered key outcomes (improvement in abdominal pain, abdominal bloating and IBS symptoms). The reviewers independently extracted data on patient characteristics, therapeutic regimens, dosage, trial duration, and outcome measures. There were no disagreements between reviewers.

### Assessment of trial quality

The methodological quality of included trials was assessed using the Jadad score [16], which judges the descriptions of randomization, blinding, and dropouts (withdrawals) in the trials. This is summarized below: a) whether randomized or not (yes =1 point, no =0), b) whether randomization was described appropriately or not (yes =1 point, no =0), c) double blind (yes =1 point, no =0), d) whether the double blinding was described appropriately (yes =1 point, no =0), e) whether withdrawals and dropouts were described or not

**Table I.** Jadad quality score of randomized controlled trials included in the meta-analysis

Study	Factors and Jadad score			total Jadad score
	randomization	blinding	withdrawals and dropouts	
Kuiken et al., 2003	2	1	0	3
Tabas et al., 2004	2	2	1	5
Vahedi et al., 2005	2	2	0	4
Tack et al., 2006	1	1	1	3
Talley et al., 2007	2	2	1	5

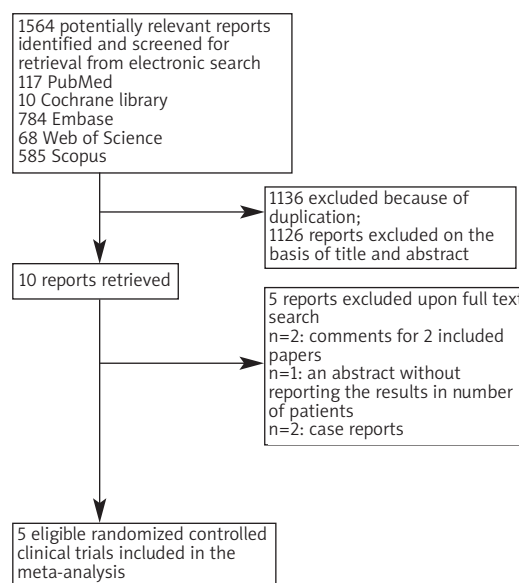
(yes =1 point, no =0). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3. The quality scores of the four RCTs are shown in Table I.

### Statistical analysis

Data from selected studies were extracted in the form of 2 × 2 tables. All included studies were pooled and weighted. The data were analyzed using StatsDirect (2.6.2). Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using the DerSimonian-Laird method. The Breslow-Day test was used to test for heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot, as an aid to explore the heterogeneity of effect estimates.

### Results

The electronic searches yielded 1564 items: 117 from PubMed, 10 from Cochrane Central, 784 from Embase, 68 from Web of Science, and 585 from Scopus. Of those, 10 trials were scrutinized in full text. Five reports were considered ineligible. Thus, 5 trials were included in the analysis (Figure 1) [11-15]. A total of 221 patients consisting of 147 (66.5%) women and 74 (33.5%) men with IBS randomized to receive either SSRI or placebo were included. Among 221 patients, 119 were treated with SSRI (41 with fluoxetine, 38 with paroxetine, and 40 with citalopram) and 102 received placebo. Improvement in abdominal pain, improvement of bloating, and improvement of IBS symptoms were evaluated in 4 [11-13, 15], 3 [11, 12, 15] and 2 trials [12, 14], respectively. Patients' characteristics, IBS subtype, type of SSRI, daily dosage of SSRI and duration of treatment for each study are shown in Table II. Improvement of abdominal pain occurred in 46.7% (49/105) of the SSRI group and 26.3% (26/99) of the placebo group. Improvement of abdominal bloating was seen in 41.9% (26/62) of the SSRI group and 25.7% (18/70) of the placebo group. Relief of IBS symptoms was reported in 61.1% (22/36) of the SSRI group and 54% (20/37) of the placebo group (Table III).



**Figure 1.** Flow diagram of the study selection process

The summary odds ratio for improvement of abdominal pain outcomes among SSRI therapy in three trials was 4.68 with a 95% CI of 0.64-34.26, a non-significant OR ( $p=0.1268$ , Figure 2a).

The Breslow-Day test for heterogeneity ( $p<0.0001$ ) indicated that the studies are significantly heterogeneous (Figure 2b) and the random effects for individual and summary of OR for meta-analysis of studies have been applied.

For 3 studies from which data for improvement of abdominal bloating outcomes among SSRI intake could be extracted, the summary OR was 2.46 with a 95% CI of 0.4-15.17, indicating a non-significant OR ( $p=0.3314$ , Figure 3a). The Breslow-Day test for heterogeneity ( $p=0.0284$ ) indicated that the studies were significantly heterogeneous and the random effects for individual and summary of OR for meta-analysis of studies have been applied (Figure 3b).

The summary odds ratio for relief of IBS symptoms outcomes among SSRI therapy in two trials was 1.31 with a 95% CI of 0.5-3.39, a non-significant OR ( $p=0.5848$ , Figure 4a). The Breslow-Day test for heterogeneity ( $p=0.7571$ ) indicated that the studies

**Table II.** Characteristics of papers included in the meta-analysis

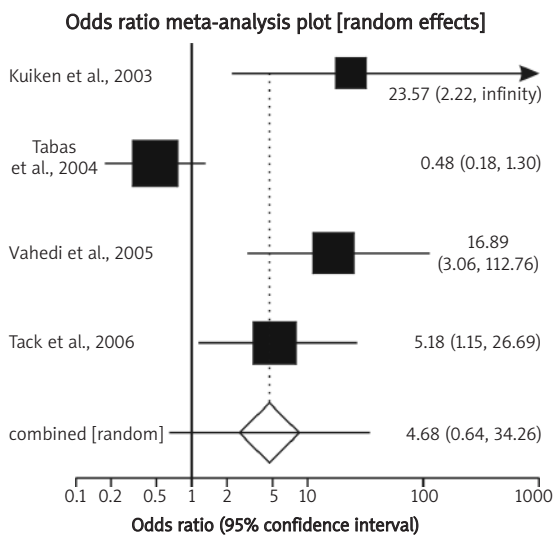
Study	Mean age	Sex (%F)	IBS subtype	Type of SSRI	Daily dosage	Treatment duration (weeks)
Kuiken et al., 2003	40	55	d-IBS, alt-IBS, c-IBS	fluoxetine	20 mg	6
Tabas et al., 2004	46	74	d-IBS, alt-IBS, c-IBS	paroxetine	10 mg	12
Vahedi et al., 2005	34.5	61	c-IBS	fluoxetine	20 mg	12
Tack et al., 2006	39	78	d-IBS, alt-IBS, c-IBS	citalopram	20 mg first 3 weeks and 40 mg second 3 weeks	6
Talley et al., 2007	ND	61	d-IBS, alt-IBS, c-IBS	citalopram	20 mg first 2 weeks and then 400 mg	12
Total	ND	66.5	d-IBS, alt-IBS, c-IBS	n=41: fluoxetine n=38: paroxetine n=40: citalopram	–	–

IBS – irritable bowel syndrome, d – diarrhoea predominant, alt – alternating, c – constipation predominant, ND – not determined

**Table III.** Outcomes of included studies

Study	Outcomes					
	improvement of abdominal pain		improvement of abdominal bloating		relief of IBS symptoms	
	SSRI	placebo	SSRI	placebo	SSRI	placebo
Kuiken et al., 2003	7/17	0/16	0/10	0/10	10/19	9/21
Tabas et al., 2004	14/43	19/38	11/30	14/38	–	–
Vahedi et al., 2005	16/22	3/22	15/22	4/22	–	–
Tack et al., 2006	12/23	4/23	–	–	–	–
Talley et al., 2007	–	–	–	–	12/17	11/16

were not significantly heterogeneous and could be combined but because of the few included papers the random effects for individual and summary of odds ratios for meta-analysis of studies have been applied (Figure 4b).

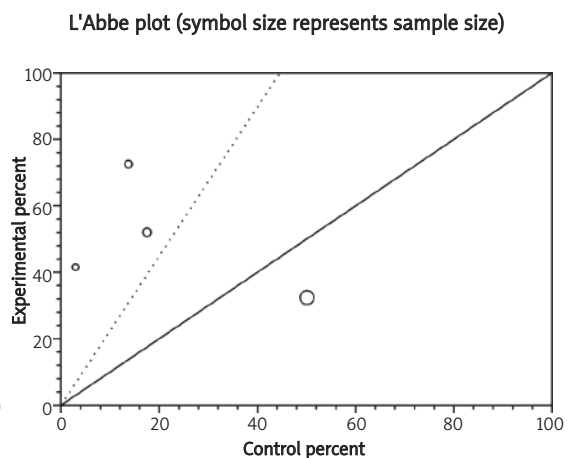


**Figure 2a.** Individual and pooled odds ratios for the outcome of “improvement of abdominal pain” in the studies considering SSRI therapy

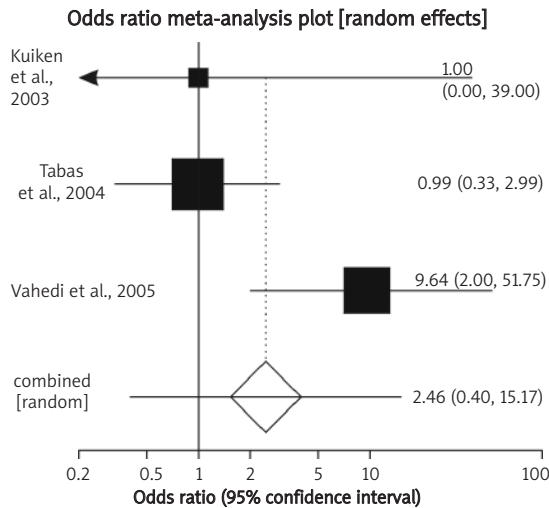
## Discussion

The results from this meta-analysis demonstrate that SSRIs do not improve abdominal pain, improve abdominal bloating, or relieve IBS symptoms significantly.

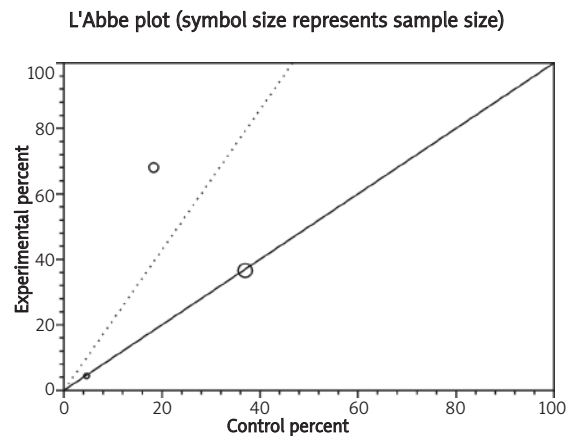
Our results showed that despite a statistically non-significant effect of SSRIs intake on improving



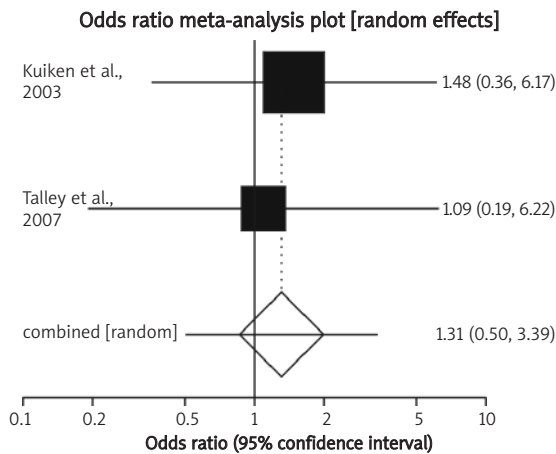
**Figure 2b.** Heterogeneity indicators for the outcome of “improvement of abdominal pain” for studies including SSRI therapy



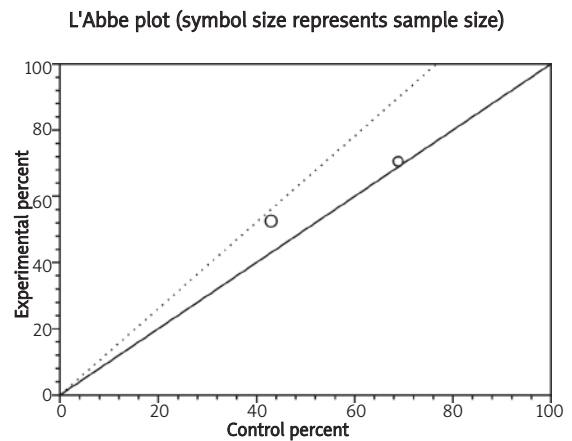
**Figure 3a.** Individual and pooled odds ratios for the outcome of “improvement of abdominal bloating” in the studies considering SSRI therapy



**Figure 3b.** Heterogeneity indicators for the outcome of “improvement of abdominal bloating” for studies including SSRI therapy



**Figure 4a.** Individual and pooled odds ratios for the outcome of “relief of IBS symptoms” in the studies considering SSRI therapy



**Figure 4b.** Heterogeneity indicators for the outcome of “relief of IBS symptoms” for studies including SSRI therapy

abdominal pain in IBS patients, a 5-fold greater efficacy of SSRIs in controlling pain is seen [12, 13, 15].

This is the first meta-analysis conducted on the efficacy of SSRIs in patients with IBS. In the current meta-analysis, all included studies fulfilled Rome criteria for IBS patients. All studies had identical inclusion and exclusion criteria and were randomized double blinded; 2 were multicentre [11, 14] and 3 were single centre trials [12, 13, 15]. All subtypes of IBS (diarrhoea predominant, constipated predominant and alternating) were incorporated in included studies. Quality of eligible studies was assessed by Jadad score. All studies have a Jadad score of 3 or more and thus all are qualified for inclusion in the meta-analysis.

However, some limitations can be noted for this meta-analysis, such as characteristics of patients (age,

sex, lifestyle, compliance, IBS subtype), type of SSRIs, dosages and treatment durations, which were somehow different in the included trials. It would have been better to individualize patients based on IBS subtypes and evaluate outcomes for each IBS subtype. Only in a study done by Vahedi et al. was this point considered, and only the constipation-predominant IBS patients were included [15].

The rationale for the use of SSRIs in IBS is based on the role of psychological stressors and mood disorders in the pathophysiology of IBS. However, in the study done by Tack et al. all included patients were non-depressed and it was shown that citalopram significantly improved abdominal pain, bloating, impact of symptoms on daily life, and overall well-being in comparison with placebo, and changes in depression or anxiety scores were not related to

symptom improvement [13]. Tabas et al. showed more improvement in overall well-being of IBS patients treated with paroxetine compared with placebo. This difference remained significant when data from non-depressed patients were analyzed separately [11]. These studies demonstrate that SSRIs exert their benefits in IBS by mechanisms other than antidepressant activity. The exact mechanisms of action of SSRIs in IBS are not completely understood at this time. There may be several mechanisms which are important in different groups of patients. The antidepressant effect is important for those patients with a depressive disorder. The most obvious action is a change in psychological processes, which leads to reduced somatisation and a reduced tendency in gut sensations as indicative of serious illness [17].

One case study suggests that SSRIs may exacerbate the symptoms of IBS. In this study, a woman with a history of IBS that had been in remission for 2 years was diagnosed for major depressive disorder and thus received sertraline. During 8 weeks, exacerbation of the symptoms of IBS occurred and after stopping sertraline she was free of IBS symptoms [18].

In conclusion it seems that SSRIs have the potential to decrease abdominal pain in IBS patients. Fortunately, recent meta-analysis indicated that SSRIs do not considerably increase the risk of major, cardiovascular, and minor malformations [19]. Thus if needed they can be administered during pregnancy by caution. However, the efficacy of SSRIs in relief of bloating and IBS syndrome based on our studies is still doubtful and needs further investigation.

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