

The placebo effect in irritable bowel syndrome trials: a meta-analysis¹

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Abstract *Background:* Despite the apparent high placebo response rate in randomized placebo-controlled trials (RCT) of patients with irritable bowel syndrome (IBS), little is known about the variability and predictors of this response.

Objectives: To describe the magnitude of response in placebo arms of IBS clinical trials and to identify which factors predict the variability of the placebo response.

Methods: We performed a meta-analysis of published, English language, RCT with 20 or more IBS patients who were treated for at least 2 weeks. This analysis is limited to studies that assessed global response (improvement in overall symptoms). The variables considered as potential placebo modifiers were study design, study duration, use of a run-in phase, Jadad score, entry criteria, number of office visits, number of office visits/study duration, use of diagnostic testing, gender, age and type of medication studied.

Findings: Forty-five placebo-controlled RCTs met the inclusion criteria. The placebo response ranged from 16.0 to 71.4% with a population-weighted average of 40.2%, 95% CI (35.9–44.4). Significant associations with lower placebo response rates were fulfilment of the Rome criteria for study entry ($P = 0.049$) and an increased number of office visits ($P = 0.026$).

Conclusions: Placebo effects in IBS clinical trials measuring a global outcome are highly variable. Entry criteria and number of office visits are significant predictors of the placebo response. More stringent entry criteria and an increased number of office visits appear to independently decrease the placebo response.

Keywords irritable bowel syndrome, meta-analysis, placebo.

INTRODUCTION

The placebo effect, therapy that is intended to have no physiological effect, may have a significant impact on the interpretation of randomized-controlled trials (RCTs).

In the field of gastroenterology, the placebo effect has been studied systematically in only a limited number of disease states. An anti-peptic drug trial found an overall placebo response rate of 55%, which was increased in men and in people of upper social classes, but did not correlate with the presence of psychological disturbances.¹ An analysis of placebo effect in 79 RCTs for the treatment of duodenal ulcer found that four times daily (q.i.d.) administration of the placebo resulted in increased healing rates compared with twice daily (b.i.d.) administration.² Ilnyckyj *et al.*³ assessed the placebo effect in 38 ulcerative colitis (UC) RCTs and found a mean placebo response rate of approximately 30%. The only variable associated with the placebo response rate in these trials was the number of office visits, which tended to increase the placebo response rate. A recent meta-analysis of the placebo response in Crohn's disease concluded that in addition to the number of office visits, duration of study and disease severity at entry influenced placebo response. The mean placebo response rate was 19%.⁴

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Received: 28 November 2004

Accepted for publication: 18 January 2005

¹Presented at the annual meeting of Digestive Disease Week, May 2004 New Orleans, LA and the Functional Brain Gut Young Investigator's Forum, April 2004 Scottsdale, AZ, USA.

High placebo response rates in irritable bowel syndrome (IBS), typically between 40 and 70%, make it difficult to detect therapeutic gain and are major concerns both for the design and interpretation of RCTs.^{5–10} The objectives of this meta-analysis are to determine the magnitude of the placebo response in IBS clinical trials and to identify factors that influence its magnitude.

METHODS

We conducted a literature search using the following databases: MEDLINE (1966–2003), OLDMEDLINE (1960–1965), PsycLIT (1960–2003), HealthSTAR (1975–2003), Cochrane Controlled Trial Register (1997–2003) and EMBASE (1985–2003).

Our search included the headings colonic diseases functional, colonic and intestinal pseudo-obstruction, and combinations of keywords such as RCTs, double-blind, random, placebo and drugs. A manual search of the references of the articles retrieved from the online search was also performed to identify additional studies. The search was limited to fully published, English language, double-blinded, RCTs, which assessed an active medication vs placebo for at least 2 weeks in 20 or more IBS patients.

A total of 96 studies met the initial inclusion criteria. Of these studies, only 45 studies had a well-defined global response outcome and ultimately were included in this analysis. The definition of a global response varied widely among studies, ranging from binary to continuous variables. Some trials recorded 'improvement vs no improvement' whereas others evaluated the Subject's Global Assessment of Relief (SGAR) with a predefined scale that characterized response to treatment. In our study, 'responders' were patients who showed a global response according to the study's definition, or, in studies lacking a global response definition, patients who showed global improvement in symptoms.

Two independent and blinded reviewers (SMP and SMO) performed data extraction. A third, independent party (AJL) reviewed the data abstractions and resolved discrepancies. The overall frequency of agreement was >95%. Study variables are grouped in the following sections: study design, demographics, global response and quality of study measures (Table 1). Of these variables, suspected predictors of the placebo effect were study duration, number of office visits (with a doctor), number of office visits/study duration, use of a run-in phase, entry criteria, study design, gender, mean age, type of active medication studied, use of invasive diagnostic procedures and quality of the study based on

Table 1 Variables assessed and recorded for each irritable bowel syndrome (IBS) trial

Study design	Parallel vs crossover Primary outcome measure Study duration Entry criteria Blinding (subject blind, investigator blind) Was there a run-in phase? Placebo treatment vs. active treatment Frequency of dosing
Study population	Total number of subjects Placebo arm Active arm Total number of subjects Completed placebo arm Completed active arm Mean age Gender distribution
Global response	Definition of a global responder Global response scale Number of responders in placebo arm (active arm)
Quality measures (Jadad) ¹¹	Was study described as double-blinded? Was study described as randomized? Were data on withdrawals and dropouts provided? Was the method of randomization described correct? Was the method of double-blinding correct?

the Jadad¹¹ scoring system. All trials, except one,¹² evaluated an oral form of therapy; therefore, route of administration was not assessed as a variable.

Statistical analyses

The meta-analysis was performed in two phases. The first phase compared the placebo response with the active response. Odds ratios (OR) were generated to compare the odds of response in placebo arm to the odds of response in active arm. Because Cochrane's Q test¹³ suggested there was evidence of heterogeneity amongst the studies ($P < 0.0001$), the DerSimonian and Laird random effects model¹⁴ was used to generate a pooled estimate of the OR. In order to identify the source of heterogeneity, potential placebo modifiers were tested as possible covariates in meta-regressions.¹⁵ Although Begg's test ($P = 0.140$)¹⁶ and Egger's test ($P = 0.071$)¹⁷ did not strictly reject the hypothesis of no publication bias, Begg's funnel plot suggested the absence of small, negative studies. As determined by influence analysis, no single trial skewed the overall results. A Spearman rank correlation test was used to

compare the active and placebo response proportions of each study.

The second phase of the meta-analysis analysed placebo responders compared with non-responders. Results from the active treatment arms were not included in this part of the analysis. Potential predictors of the placebo response across studies were tested one at a time as covariates in population-weighted regression analyses. This technique is comparable with the method used in the placebo analysis by Ilnyckyj *et al.*³ This phase of the meta-analysis was used to identify potential predictors of the placebo response. Studies were population weighted according to their sample size. All analytic computations were performed using STATA version 8.2.¹⁸

RESULTS

The characteristics of the 45 studies that met the inclusion criteria are shown in Table 2. A total of 7101 subjects were included, of whom 3352 received placebo. The population-weighted mean (95% CI) of proportion of the patients who responded to placebo was 40.2% (35.9–44.4) with a range from 16 to 71%. Response rates in the active arm ranged from 28.0 to 93.3% and with a population-weighted mean of 54.1% (48.5–59.8). The pooled OR, defined as the odds of response to placebo compared with the odds of response to the active medication, was 0.55% (0.45–0.67; Fig. 1). A modest, but significant, positive correlation was present between the response rate to an active treatment and the placebo (Fig. 2; Spearman rank correlation = 0.3647; $P = 0.0138$).

Modifiers of the placebo response

The population-weighted mean placebo response was 37.6% (32.9–42.3) in studies that used the Rome criteria ($n = 15$) as an entry criteria and 46.5% (39.1–53.9) in studies that used the Manning or other unspecified criteria ($n = 30$). The decrease of the placebo response was an average of 8.9% [(0.03–17.8), $P = 0.049$]. The placebo response declined significantly with a greater number of office visits. Each additional visit was associated with 4.4% (0.6–8.3) reduction in the placebo response rate. After removal of the study by Rajagopalan *et al.*¹⁹ with the greatest number of office visits ($n = 12$), the results remained significant and substantively the same in magnitude. Study duration and the number of visits/study duration did not significantly influence the placebo response. Use of a run-in phase showed a trend towards a decrease in the placebo response, these results did not reach statistical

significance ($P = 0.064$). The other variables assessed (Table 3) were not significant predictors of the placebo response.

When the potential placebo predictors were tested for an association with the odds of response to placebo compared with active treatment (first phase of the meta-analysis), none of the variables was significant.

DISCUSSION

Comparison of active treatment with placebo in RCTs is considered the 'gold standard' for methodological rigour. A placebo is traditionally defined as an inactive substance or other form of sham therapy, which is identical in appearance and method of administration to the active treatment. Goals of placebo-controlled studies are to adequately control for variations in natural history of disease progression, regression to the mean, if blinded, for recognition bias. Understanding of the placebo effect is especially important in functional disorders such as IBS where variations in response to treatments are high. To the best of our knowledge, this is the first meta-analysis of the placebo effects in IBS trials.

Based on our review of 45 IBS RCTs we found an average placebo response rate of 40.2%. By comparison, the mean placebo response rates in RCTs in patients with inflammatory bowel disease (IBD) population has ranged from 19⁴ to 30%.³ Our findings for IBS trials are similar to those in depression,²⁰ chronic pain,^{21,22} erectile dysfunction²³ and dyspepsia.²⁴ Our study attempts to characterize the effects of study design on the placebo effect in an effort to understand this phenomenon better.

We evaluated 11 variables as potential predictors of the placebo effect and identified two that were significantly associated with the magnitude of the placebo effect. Lower placebo response rates were found in trials that used fulfilment of Rome I or II criteria as an entry criterion compared with trials that used Manning or other more permissive criteria. This finding may correspond to the observation that prevalence rates of IBS vary according to the definition of IBS used.²⁵ Studies that used the Rome criteria were all published within the past decade and, in general, are large, high-quality, multicentre studies. Use of the Rome criteria may be associated with a lower placebo response because it leads to a more homogenous study population with a confirmed diagnosis of IBS.

A lower placebo response also corresponded with an increasing number of office visits. These results are in contrast to the findings of Ilnyckyj *et al.*³ who looked at studies of UC patients. Ilnyckyj *et al.*³ found that

Table 2 Characteristics of the 45 trials included in the meta-analysis

Author	Year of publication	Active medication studied	Study design	Entry criteria	Placebo arm (N)	Office visits (N)	Study duration (weeks)	Responders in placebo arm (%)	Responders in active arm (%)
Soltoft <i>et al.</i> ³⁶	1976	Psyllium	Parallel	Other	23	N/A	6	65	52
Milo ³⁷	1980	Domperidone	Parallel	Other	32		4	34	79
Fielding ³⁸	1980	Trimethoprim	Parallel	Other	27	6	24	63	54
Longstreth <i>et al.</i> ³⁹	1981	Psyllium	Parallel	Other	34	4	8	71	77
Fielding ⁴⁰	1981	Timolol	Parallel	Other	37	3	24	65	54
Page and Dimberger ⁴¹	1981	Dicyclomine hydrochloride	Parallel	Other	37	1	2	54	82
Guslandi <i>et al.</i> ⁴²	1981	Octatropine + diazepam	Parallel	Other	20	4	6	40	80
Fielding ⁴³	1982	Domperidone	Parallel	Other	28	2	12	57	64
Golechha <i>et al.</i> ⁴⁴	1982	Ispaghula husk	Crossover	Other	26	1	3	23	50
Myren <i>et al.</i> ⁴⁵	1982	Trimipramine	Parallel	Other	31	2	4	70	83
Arthurs and Fielding ⁴⁶	1983	Ispaghula husk	Parallel	Other	38	2	4	63	73
Tripathi <i>et al.</i> ⁴⁷	1983	Trimipramine	Parallel	Other	25	6	5	16	28
Chadda <i>et al.</i> ⁴⁸	1983	Diphenylhydantoin	Crossover	Other	25	2	3	20	48
Dew <i>et al.</i> ⁴⁹	1984	Peppermint oil	Crossover	Other	29	2	2	17	83
Nash <i>et al.</i> ⁵⁰	1986	Peppermint oil	Crossover	Other	33	1	2	52	61
Ghidini <i>et al.</i> ⁵¹	1986	Rociverine + trimebutine	Parallel	Other	30	3	8	67	68
Prior and Whorwell ⁵²	1987	Ispaghula husk	Parallel	Other	25	3	12	52	81
Lucey <i>et al.</i> ⁵³	1987	Bran biscuits	Crossover	Manning	14	3	12	71	79
Greenbaum <i>et al.</i> ⁵⁴	1987	Desipramine	Crossover	Other	28	?	6	18	54
Prior <i>et al.</i> ⁵⁵	1988	Lidamide	Crossover	Other	70	2	2	21	26
Centonze <i>et al.</i> ⁵⁶	1988	Cimetopramine	Parallel	Other	21	6	24	24	87
Gilvray <i>et al.</i> ⁵⁷	1989	Pirenzapine	Parallel	Other	11	1	4	56	45
Yadav <i>et al.</i> ⁵⁸	1989	Clidnium/librium/ ispaghula husk	Parallel	Other			6	33	44
Dobrilla <i>et al.</i> ⁵⁹	1990	Cimetopramine	Parallel	Other	34	3	12	68	89
Van Outryve <i>et al.</i> ⁶⁰	1991	Cisapride	Parallel	Other	28	4	12	65	72
Fowle <i>et al.</i> ⁶¹	1992	Wheat bran	Parallel	Rome I	19	5	12	68	61
Snook and Shepherd ⁶²	1994	Insoluble bran fibre	Crossover	Other	20	1	7	55	53
Cann <i>et al.</i> ⁶³	1994	Loxiglumide	Parallel	Other	77	N/A	8	32	
Mathias <i>et al.</i> ¹²	1994	Leuprolide	Parallel	Other	15	3	12	40	93
Efskind <i>et al.</i> ⁶⁴	1996	Loperimide	Parallel	Other	34	N/A	5	74	66
Schutze <i>et al.</i> ⁶⁵	1997	Cisapride	Parallel	Rome I	48	3	12	71	67
Battaglia <i>et al.</i> ⁶⁶	1998	Otilimum bromide	Parallel	Rome I	133	3	15	50	65
Farup <i>et al.</i> ⁶⁷	1998	Cisapride	Parallel	Rome I	34	3	12	59	39
Rajagopalan <i>et al.</i> ¹⁹	1998	Amitriptyline	Parallel	Rome I	11	12	12	27	64
Camilleri <i>et al.</i> ⁶⁸	2000	Aloesteron	Parallel	Rome I	240	3	12	51	54
Muller-Lissner <i>et al.</i> ⁶⁹	2001	Tegaserod	Parallel	Rome I	251	3	12	35	46
Lembo <i>et al.</i> ⁷⁰	2001	Aloesteron	Parallel	Rome II	219	3	12	30	57

(Continued overleaf)

Table 2 (Continued).

Author	Year of publication	Active medication studied	Study design	Entry criteria	Placebo arm (N)	Office visits (N)	Study duration (weeks)	Responders in placebo arm (%)	Responders in active arm (%)
Camilleri <i>et al.</i> ⁷¹	2001	Aloesteron	Parallel	Rome I	247	4	12	26	59
Novick <i>et al.</i> ⁷²	2002	Tegaserod	Parallel	Rome I	591	3	12	39	44
Hubner and Moser ⁷³	2002	Activated charcoal	Parallel	Rome I	131	3	12	53	60
Glende <i>et al.</i> ⁷⁴	2002	Otilinium bromide	Parallel	Rome I	134	3	12	22	37
Olden <i>et al.</i> ⁷⁵	2002	Aloesteron	Parallel	Rome I	203	3	8	45	69
Mitchell <i>et al.</i> ⁷⁶	2002	Alverine citrate	Parallel	Rome II	54	4	12	44	50
Hawkes <i>et al.</i> ⁷⁷	2002	Naloxene	Parallel	Rome II	13	N/A	8	27	43
Camilleri <i>et al.</i> ⁷⁸	2003	Clonidine	Parallel	Rome I	13	N/A	4	46	40
								Population-weighted mean 40.2	Population-weighted mean 54.1

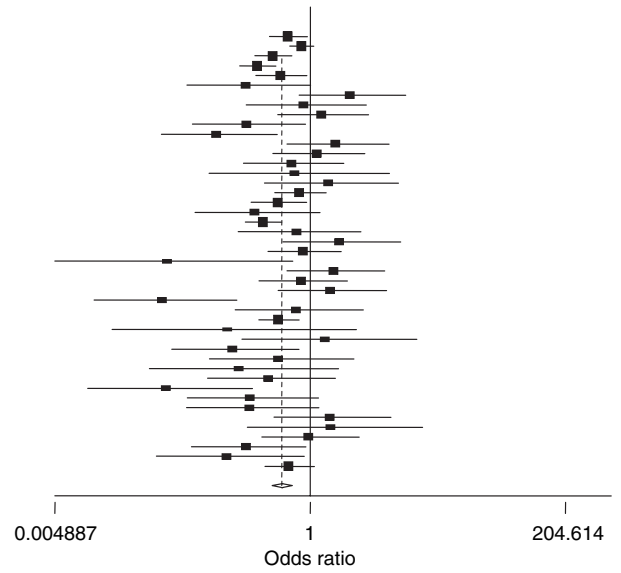


Figure 1 Pooled analysis using the DerSimonian and Laird¹⁴ random effects model to generate a pooled odds ratio (OR) defined as odds of response to placebo/odds response to active medication in the 45 trials.

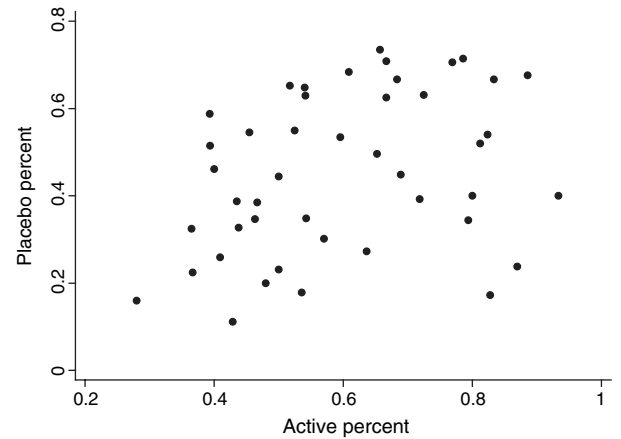


Figure 2 Scatter plot of active arm global response (% in x-axis) vs the placebo arm (% in y-axis). The Spearman rank correlation of 0.3647 ($P = 0.0138$) indicates a significant, positive correlation between the active and placebo arm responses.

studies with three or more office visits had an increased placebo response in comparison to studies with three or fewer office visits. Our findings are counterintuitive as clinical experience shows that a strong patient–doctor relationship improves clinical outcome. In order to ensure the accuracy of these results all the studies included in the meta-analysis were re-examined with a focus on the number of office visits. Our criteria used to identify the number of office

Table 3 Associations of study variables with the magnitude of the placebo response

Variable	<i>P</i> -value
Study design (parallel vs crossover)	0.530
Study duration	0.948
Use of a run-in phase	0.064
Jadad score	0.704
Entry criteria	0.049
Number of office visits	0.026
Number of office visits/study duration	0.235
Use of diagnostic testing	0.356
Gender (percentage of female)	0.403
Mean age	0.146
Type of active medication	0.139

criteria were stringent and demanded that the authors of each study explicitly state the number of visits in the text. If less stringent criteria were used to identify the number of office visits then the results may vary from those that we recorded. Although there is no obvious explanation for these findings, possible causes could include: (i) increased interaction with an investigator who is not the patient's primary doctor or gastroenterologist may have a negative effect on patients, and/or (ii) a greater number of office visits may be associated with inadequate blinding, which in turn, may lead to a drop out of patients who suspect they are receiving placebo and/or (iii) the increased possibility of expression of disappointment that extra visits allowed when participants obtained insufficient relief as the trial progressed.

Our findings show a trend towards a decreased placebo response in trials that used a run-in phase compared with those that did not. The purposes of a placebo run-in are to establish compliance (so that those who are later randomized are more likely to adhere to protocol) or to eliminate participants who respond to the placebo during run-in (thereby, decreasing placebo response rates in the RCT and reducing sample size needs for detecting a difference in outcomes between active vs placebo groups). The elimination of placebo responders during a run-in has recently been the subject of much controversy.^{26–29} Our findings suggest that further investigation in their utility is warranted.

Components of the patient–doctor relationship (e.g. attention, compassion, positive expectation, reassurance, etc.), natural history of the disease, regression to the mean, and measurement error may each contribute to the placebo effect seen IBS trials. Interestingly, a meta-analysis of 114 clinical trials across 40 different conditions that had included both placebo and no treatment arms found little or no evidence for a

placebo effect beyond no treatment-natural history.³⁰ Studies that used a continuous subjective outcome measure and studies for the treatment of pain showed a small placebo benefit over and beyond natural history while studies that used a binary outcome and objective outcome measure showed no benefit. Unfortunately, our study can shed no light on this issue as none of the included IBS studies had a natural history wait list arm. Such a determination is critical to a fuller understanding of the placebo effect in IBS.

Our study has at least four limitations. Firstly, there was significant heterogeneity among the studies. Differences in patients, treatments, measures of outcome and study design likely contribute to the variations in placebo effect we observed. Our decision to limit the analysis to studies that included a clearly defined global response helped to reduce heterogeneity. Moreover, this decision reflected the Rome committee recommendations that the primary outcome measure of IBS trials be a single global clinical rating.^{31–35} Nonetheless, the definition of a global responder varied among trials.

A second limitation is that our meta-analysis is limited to published studies. Our results suggest possible publication bias in that smaller negative studies were not being published. These studies likely also had a significant placebo effect and therefore may have increased the average placebo response percentage in the pooled results. Moreover, published studies did not provide individual level data on patient characteristics. Data on each person's age, gender, medical history and symptom severity would have been helpful to better understand the characteristics of placebo responders.

In conclusion, this analysis has many implications for future IBS study design. The placebo response rate in IBS trials is approximately 47% however, if the Rome I or II entry criteria are used to define IBS then the response rate lowers to approximately 38%. We suggest that trials create stringent entry criteria to help minimize the placebo response. The number of office visits may also influence the placebo response with a decreased response with increased visits. In the end, it is likely interplay between study design and individual patient characteristics that engenders the placebo response. Both components need to be explored further, but presently, this analysis illuminates the challenges of the placebo effect in IBS trials and defines new predictors of the placebo response.

ACKNOWLEDGMENT

This study was supported in part by NCCAM/NIDDK-NIH grant #1 R01 AT01414-01 and NCCAM/OBSSR-NIH grant #1 R21 AT002860-01.

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