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Effects of 5-HT$_3$ Antagonists on Symptom Relief and Constipation in Non-constipated Irritable Bowel Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background & Aims—We performed a systematic review and meta-analyses to estimate treatment efficacy and constipation rate of 5-HT$_3$ antagonists in patients with non-constipated (NC) or diarrhea-predominant (D) -IBS.

Methods—Two reviewers independently searched MEDLINE, EMBASE, and Web of Science (1966 to December 15th 2006) for randomized controlled trials (RCTs) of 5-HT$_3$ antagonists in IBS reporting clinical endpoints of the IBS symptom complex and safety parameters. Study characteristics, markers of methodological quality, and outcomes for the intention-to-treat population for each RCT were extracted independently.

Results—We found 14 eligible RCTs of alosetron (n=3024) or cilansetron (n=1116) vs. placebo (n=3043) or mebeverine (n=304). Random effects meta-analyses found 5-HT$_3$ antagonists more effective than the comparators in achieving global improvement in IBS symptoms (pooled relative risk 1.60, 95% CI 1.49, 1.72; I^2=0%) and relief of abdominal pain and discomfort (pooled relative risk 1.30, 95% CI 1.22, 1.39, I^2=22%). Benefit was apparent for both agents, in patients of either sex. These agents were more likely to cause constipation (pooled relative risk 4.28, 95% CI 3.28, 5.60, I^2=65%); there was less constipation with 5-HT$_3$ antagonists in D-IBS patients than in mixed populations (NC- and D-IBS; ratio of RR 0.65, 95% CI 0.41, 0.99). Nine patients (0.2%) using 5-HT$_3$ antagonists had, at least, possible ischemic colitis versus none in control groups.

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Disclosures: Dr. V. Andresen has served as a consultant for Solvay, the manufacturer of cilansetron, from 2004 to 2005 and was employed in the medical department of the German affiliate of GlaxoSmithKline, the manufacturer of alosetron, from 2000 to 2001. Dr. M. Camilleri received research support in 2006 to 2007 for a single-center pharmacodynamic study with a drug not in the 5-HT3 antagonist class from GlaxoSmithKline, manufacturer of alosetron, and has served as a consultant in 2006, receiving annually less than the federal threshold for significant financial conflict of interest.
Dr. J Keller has served as a consultant for GlaxoSmithKline from 2000 to 2001.
Dr. P. Layer has served as a consultant for GlaxoSmithKline from 2000 to 2001 and for Solvay from 2004 to 2005.

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Conclusions—5-HT_3 antagonists significantly improve symptoms of NC- or D-IBS in men and women. There is increased risk of constipation with 5-HT_3 antagonists, although the risk is lower in those with D-IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent functional gastrointestinal disorder affecting 3 to 15 % of the general population[1–3]. It has a substantial impact on morbidity and quality of life[4]. It is characterized by unexplained abdominal pain, discomfort, and bloating in association with altered bowel habits[5]. The pathophysiology of IBS is not well understood, but evidence of abnormal gastrointestinal motor function, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system and the brain-gut axis.

Serotonin (5-HT) is an important neurotransmitter in the brain-gut axis and is involved in several functions of the gastrointestinal (GI) tract including the peristaltic reflex [6]. At least seven different 5-HT receptor types have been described [7]. 5-HT_3 receptors are present both centrally and peripherally in the brain-gut axis, and 5-HT_3 antagonists have been shown to reduce responses to noxious gut stimuli in animals [8–11].

Two 5-HT_3 antagonists have been developed to date for the treatment of IBS, alosetron and cilansetron. Alosetron is approved and available in the United States; cilansetron has undergone a large phase III trial program, but is not yet approved. Several studies in healthy individuals and IBS patients have demonstrated significant differences in the effects of these two 5-HT_3 antagonists versus placebo with respect to a wide range of outcomes. These include sensory ratings or thresholds for perception in response to gut distention [12], postprandial symptoms [13], gastrointestinal transit [14, 15], and bowel function, including more solid stool consistency and decreased stool frequency and urgency.

Clinical phase II and III trials have demonstrated superiority of alosetron or cilansetron over placebo, and over an alternative IBS treatment (mebeverine) in one study, with respect to the specific primary endpoints used in each study [16–22]. However, the primary endpoints varied across studies. Thus, while earlier studies used ‘relief of abdominal pain or discomfort’ as a primary feature of the symptom complex of IBS [5], subsequent studies followed the recommendations of the consensus Rome documents [23] and used ‘global symptom improvement’ to capture the breadth of bothersome symptoms. Current evidence suggests that such binary endpoints of symptom relief are able to assess therapeutic efficacy of drugs in clinical trials of IBS [24].

Few studies have also evaluated the effect of 5-HT_3 antagonists on quality of life [18] or patient satisfaction [25].

Since 5-HT_3 antagonists delay GI transit [26], the main adverse effect of this drug class is constipation. While earlier studies included IBS patients with non-constipated bowel habits (NC-IBS), later trials focused on diarrhea-predominant IBS (D-IBS).

An earlier meta-analysis of studies with the 5-HT_3 antagonist alosetron showed beneficial effects in women with non-constipated IBS [27]. Since that publication, further trials using different 5-HT_3 antagonists and including male patients have been performed. The hypothesis of this study was that the drug class of 5-HT_3 antagonists is superior to placebo or other comparators in improving endpoints of the IBS symptom complex in both men and women with non-constipated IBS.

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Hence, the aim of the present systematic review and meta-analysis was to estimate the effects of 5-HT_3 antagonists on 'relief of abdominal pain or discomfort' or on 'global IBS symptom improvement' and on constipation in patients with non-constipated or diarrhea-predominant irritable bowel syndrome.

METHODS

The present meta-analysis was performed and reported according to the standards of the QUOROM statement [28].

Eligibility Criteria

We included randomized controlled trials evaluating the effect of 5-HT_3 antagonists on 'relief of abdominal pain and discomfort' or 'global improvement of IBS symptoms'.

Exclusion criteria were based on type of study (e.g. review, animal study, basic research), study endpoints (e.g. pharmacodynamic endpoints), duplicate publication, and indication (i.e. non-IBS studies). Neither publication status nor language of publication was an exclusion criterion.

Search Strategy

We designed comprehensive computer-based searches of the electronic databases MEDLINE (1966 - December 15, 2006) and EMBASE (1988 - December 15, 2006). Terms used for the computer-based search included: *serotonin, 5-HT, alosetron, cilansetron, irritable bowel syndrome, therapy, clinical trial, diarrhea-predominant, and functional bowel disease*. Using Web of Science (1990 - December 15, 2006) we sought relevant abstracts in order to identify unpublished trials. We also reviewed the reference sections of included trials. The search strategy, including key words and steps followed, are included in Appendix I (on-line manuscript).

Study Selection

Two investigators (V.A, J.K.), working independently and in duplicate, selected and evaluated study eligibility. κ statistic was used to test for chance-adjusted inter-observer agreement on study eligibility. One investigator (M.C.), who had participated in the planning, design, analysis and interpretation of three of the included trials [19, 29, 30], did not participate in the process of retrieval, trial selection or in tabulation and statistical analysis of the data for this review.

Data Collection

For each study, we assessed the participants' IBS type according to the declared abnormal bowel function, mean age and gender, treatment regimen used (daily dosage and duration of treatment), number of patients lost to follow up and adequacy of randomization and blinding of patients, clinicians and investigators. Then, we extracted the intention-to-treat data for the efficacy and safety analyses.

For the assessment of the primary efficacy parameters, we used the proportion of patients responding to treatment as defined in the individual trials with regard to either 'relief of abdominal pain and discomfort' or 'global improvement of IBS symptoms'. Most studies used weekly binary assessments of "yes/no-improvement" or "yes/no-adequate relief" to define responders. A few studies used either a visual analog scale (VAS) or a 7-point Likert scale to assess symptom improvement, and the studies included a definition of the cut-off on this scale to define responders [17, 31, 32]. For the purpose of our analysis, we incorporated the individual study's definition of a responder when a VAS or Likert scale was used.

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For studies that did not report an overall response rate, but presented separate numbers of responders for different treatment periods (e.g. number of responders in each month), we averaged the period response rates.

For the safety analysis, we used the number of patients reporting constipation and ischemic colitis per treatment group during the overall treatment period.

Quality Assessment

Two independent investigators (V.A., J.K.) evaluated the quality of the studies according to quality criteria suggested for randomized controlled trials (Table 1)[33].

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Two papers of alosetron studies [30, 34], which included NC-IBS and D-IBS patients, reported the constipation results for all included patients but the efficacy results only for the D-IBS population. We contacted GlaxoSmithKline, the pharmaceutical company that conducted all clinical trials with alosetron. GlaxoSmithKline kindly provided us with the efficacy results for the complete study population of these studies as well as with additional information regarding the alosetron study by Krause et al.[35], published only in abstract form as of the date of this systematic review.

Statistical Analysis

The meta-analytic comparison was based on the crude unadjusted relative risk (RR) of treatment response or constipation. Using a random effects model, we estimated the pooled RRs for improvement of 'pain and discomfort', 'global IBS symptoms' and pooled RRs for constipation and their corresponding 95% confidence intervals (CI). We used I^2 statistic quantifying between-study inconsistency as the proportion of the overall variability across studies that is not due to chance (random error) [36] to evaluate heterogeneity. One convention considers I^2 <25% as reflecting small inconsistency and >50 % as large inconsistency across studies [36]. While we report meta-analytical estimates for constipation, we report the total number of patients with ischemic colitis across all studies.

Subgroup Analyses

To explore potential causes of between-study inconsistency, we pre-specified several subgroup analyses with tests of interaction [37]. We explored subgroups based on study populations (NC-IBS versus D-IBS only), sex (women, men or mixed population), medication used, dose (standard vs. higher than the standard), treatment duration (12 weeks versus long-term, i.e. 24 or 48 weeks), and comparator (vs. placebo or vs. active comparator). We also explored subgroup analyses based on outcome definition (dichotomous 'yes/no improvement' versus Likert or visual analog scales with pre-specified cut-offs to define responders) and outcome estimation (reported overall response rates versus calculated average response across periods). Finally, we explored subgroup analyses by publication status (abstract only versus full text manuscript).

RESULTS

Flow of Study Retrieval

Figure 1 describes the study identification and selection process. Reasons for exclusion included the type of study (review, animal study, basic research, and review and analysis of already included trials and post-marketing data), the study endpoints (pharmacodynamic endpoints, quality of life, patient satisfaction, patient adherence to therapy), duplicate

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publication (e.g. of other endpoints such as quality of life) of studies that were already included, and the indication (functional dyspepsia instead of IBS).

Ten full reports of randomized controlled trials with the 5-HT_3 antagonist alosetron met the inclusion criteria [17, 19, 20, 29–32, 34, 38, 39], one of which reported only safety data [39]. We also found 4 eligible abstracts, one trial with alosetron [35] and three trials with cilansetron [21, 22, 40]. Overall this review includes 14 trials (n=7984 patients, 3221 randomized to alosetron 1 mg bid, 1116 to cilansetron 2mg tid, 3343 to placebo and 304 to mebeverine 125 mg tid as comparator). The κ statistic for chance-adjusted inter-observer agreement on study eligibility was 0.86.

Study Characteristics

Table 2 summarizes the principal characteristics of the 14 eligible trials. The 10 full reports met all quality criteria (Table 1). For the studies not published as full papers, only partial assessment of quality parameters was possible. Overall, all studies excluded constipation-predominant IBS and focused on recruiting non-constipated IBS patients. Eight studies included only D-IBS patients [17, 21, 22, 29, 32, 35, 38, 40] while 6 studies included both D-IBS and NC-IBS [19, 20, 30, 31, 34, 39]. The published manuscript of two of these studies [30, 34] reported only the efficacy outcomes for the D-IBS subpopulation, but GlaxoSmithKline provided results for the complete study population, i.e. D-IBS and NC-IBS. Most of the alosetron studies included only women, consistent with the decision to explore efficacy of alosetron exclusively in women in the phase III program given the lack of efficacy in men in the earlier phase IIB study [19]. A later study exclusively tested the efficacy of alosetron in men [38]. While the cilansetron studies included both women and men with a planned ratio of 2:1 [21, 22, 40]; the abstracts did not report the actual proportion in each treatment arm.

The doses used in most studies were standard (alosetron, 1 mg twice a day; cilansetron, 2 mg three times a day); however 4 trials of alosetron used several dosages [19, 31, 35, 38], and one of these dose-response studies (a phase IIb study) did not include what would eventually be the approved standard dose [31]. From this study we extracted for analysis the results corresponding to a higher dosage (2 mg twice a day) and a lower dosage (0.5 mg twice a day) relative to the standard dosage, and tested the influence of either choice in our overall results.

Efficacy Endpoints

Relief of abdominal pain and discomfort

Meta-analyses: Table 3 and Figure 2 show the results of this meta-analysis and of the subgroup analyses by drugs (alosetron and cilansetron). The overall pooled estimated RR was 1.30 (1.22, 1.39) in favor of 5-HT_3 antagonist treatment. The calculated number needed to treat (NNT) was 7.7 and the overall risk difference was 0.13 (0.1, 0.16). The results were consistent across studies (I^2=22%). Also, the results were consistent across choice of dose for the Bardhan et al trial [31].

Subgroup analyses: There were three significant subgroup-treatment interactions (Table 5a). In these three interaction tests, the composition of the comparison groups largely overlapped. First, there was a lower RR in the alosetron subgroup (1.23 [1.15, 1.32]) compared to the cilansetron subgroup (1.43 [1.29, 1.59]) with a relative risk ratio (RR-ratio) of 0.86 [0.76, 0.98]. Second, there was a lower RR for studies including women only (1.23 [1.14, 1.32]) compared to studies including both genders or only men (1.39 [1.28, 1.51]) with a RR-ratio of 0.88 [0.76, 0.98]. Third, there was a lower RR for full papers (1.23 [1.14, 1.32]) compared to studies published as abstracts only (1.41 [1.29, 1.54]) with a RR-ratio of 0.87 [0.78, 0.98]. The test for interaction was not significant for the other subgroup analyses (Table 5a).

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Global improvement of IBS symptoms

Meta-analyses: Table 3 and Figure 3 show the results of this meta-analysis and of the subgroup analyses by drugs (alosetron and cilansetron). The overall pooled estimated RR was 1.60 (1.49; 1.72) in favor of 5-HT_3 antagonist treatment. The calculated NNT was 4.2 and the overall risk difference was 0.22 (0.18, 0.25). The results were consistent across studies (I^2=0%).

Subgroup analyses: There was a significant subgroup-treatment interaction for the treatment duration with a higher RR for this efficacy endpoint in the 12-week subgroup (1.64 [1.29, 1.51]) compared to the 24-week subgroup (1.33 [1.16, 1.52]) and a RR-ratio of 1.23 [1.05, 1.44]) (Table 5b). The tests of interactions were not significant for all other subgroup analyses including the publication type (full text or abstract; Table 5b).

Safety Endpoints

Constipation—Most cases of self-reported constipation in these trials were considered mild to moderate in severity. Approximately 10 to 43% of the participants who developed constipation withdrew from the trials for this reason. In all of these cases, constipation reportedly resolved rapidly after stopping the treatment. None of the studies reported serious complications due to constipation.

Meta-analyses: Table 4 and Figure 4 show the results for the RR of constipation and the RR-ratio of the subgroup analysis by study population (D-IBS only versus NC- and D-IBS). Participants were more likely to report constipation in the intervention group (pooled RR 4.28 [3.28; 5.60]) than in the placebo or mebeverine groups, although RR estimates were heterogeneous across trials (I^2 = 65%). The calculated overall number needed to harm (NNH) was 4.7 and the overall risk difference was 0.17 (0.14, 0.21). The heterogeneity between trials may reflect differences in recording the occurrence of constipation. Constipation was typically reported as an adverse event based on the self-report of patients. However, this was not specified in all trials. In some studies, bowel diaries were also used to identify constipation.

Subgroup analyses: Table 6 shows that the risk for constipation was lower in the studies including D-IBS only (RR 3.6 [2.56, 5.05]; risk difference 0.16 (0.11, 0.22); NNH 5.6) compared to the studies including both NC- and D-IBS (RR 5.58 [4.27, 7.3]; risk difference 0.2 (0.16, 0.23); NNH 4.5) with a significant RR-ratio of 0.65 [0.41, 0.99]. There was also a significant RR-ratio for abstracts versus full papers (0.60 [0.36, 0.98]). Since all abstracts included only D-IBS patients, there is an overlap with the subgroup analysis for the included study population. *Post hoc* analyses revealed that Chang et al [38], the only study exclusively enrolling men, reported no cases of constipation in the control group and a proportion of constipation in the treatment group similar to that observed in the other trials. Exclusion of this outlier trial yielded an RR for constipation of 4.19 [3.23; 5.45].

Ischemic colitis—There were 9 cases of at least possible ischemic colitis in the 5-HT_3 antagonist treatment group (0.2%) and 0 in the control group (RR 16.01 [0.93, 275]; p=0.06).

DISCUSSION

Main Findings

This systematic review of large randomized controlled trials indicates that 5-HT_3 antagonists, as a class, significantly improve abdominal pain and discomfort and global IBS symptoms in patients with NC- or D-IBS. Treatment response was consistent across a range of studies performed in different countries with an estimated pooled RR of 1.60 [1.49, 1.72], a NNT of 4.2 and a risk difference of 0.22 [0.18, 0.25] for the ‘improvement of global IBS symptoms’, and an estimated pooled RR of 1.30 [1.22, 1.39], a NNT of 7.7 and a risk difference of 0.13

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[0.10, 0.16] for the 'relief of abdominal pain and discomfort'. The effect of treatment appeared quite similar in men and women (RR of 1.39 for men or both genders vs. 1.23 for women only).

For the endpoint "relief of abdominal pain and discomfort", there were significant subgroup-treatment interactions for the different drugs (alosetron vs. cilansetron), the included gender (female only vs. male or mixed gender) and the publication type (full paper vs. abstract). However, since all cilansetron studies included both men and women and were only available as abstracts, subgroup inferences are confounded. The only significant subgroup-treatment interaction influencing the RR for the other efficacy outcome "global improvement of IBS symptoms" was treatment duration, with a lower RR in the long-term group. This could suggest that the treatment effect might wear off over time. However, the fact that there was only one study with treatment for 24 weeks compared to 6 studies with treatment for 12 weeks does not allow a definite conclusion as to whether the treatment efficacy wanes with time.

Eligible trials reported constipation rates of 20–30% in the treatment group. The risk for constipation was lower in trials including only patients with D-IBS compared to the studies including patients with both NC- and D-IBS with a significant subgroup-treatment interaction, indicating that patients with D-IBS may have a more favorable benefit/risk ratio of 5-HT_3-antagonist treatment.

Limitations and Strengths

Limitations and strengths of this systematic review pertain to the primary data and the review itself. It is a limitation of the primary data that four studies (including all three studies with cilansetron) were only available as abstracts at the time of this analysis and their methodological quality could not be fully evaluated. The majority of included trials (10 of 14), however, were high quality trials published in full. Another strength of the primary data is that all studies used comparable, standardized endpoints and similar trial designs.

Regarding limitations of the review, we cannot exclude publication bias and reporting bias. To some extent, the involvement of one of the authors (M.C.) with the alosetron program allows us to be more confident that we included all conducted trials with this compound. Moreover, the funnel plot analysis did not indicate publication bias (Figure 5), although this type of analysis may sometimes be misleading [41]. We still may have missed small trials and trials that were only published in abstract form. In terms of reporting bias, all eligible trials informed the safety outcomes, but one of which did not inform the efficacy outcomes [42]. Another limitation is that the estimated relative risk is calculated on the basis of published papers and abstracts, particularly those on cilansetron. It is also unclear whether the greater efficacy in men than women is due, in part, to the typically smaller number of males in IBS studies that included both genders (even though this is not reported in the abstracts on cilansetron) or the fact that several studies with alosetron excluded males.

The main strength of this review is its comprehensive approach. First, we included four studies only available as abstracts. Exclusion of these abstracts would have led to increases in random error and in publication bias since these were large multicenter trials including more than 2500 patients and were of high quality regarding randomization and blinding and sufficiently defined the study populations and outcomes. Moreover, abstracts provided the only available data for the one of the two 5-HT_3 antagonist drugs, cilansetron, evaluated for efficacy and safety in large multicenter IBS trials. Second, by including studies of both alosetron and cilansetron, this review has combined all available randomized controlled trials on 5-HT_3 antagonists in the treatment of NC-IBS regarding the main clinical endpoints. This strengthens the validity of the results with regard to the effects of this class of drugs in the treatment of NC-IBS.

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Comparison with Other Studies

The observation of similar efficacy of these agents in men and women in the meta-analysis is in contrast to earlier suggestions that this drug class might be ineffective in men, which were based on an early phase IIB trial in the drug development of alosetron that failed to show significant treatment effect in men [19]. However, there were only few men included in that study and the negative results could be explained by a type II error, as openly acknowledged by the authors of that study. Subsequent phase II and III trials with alosetron were restricted to women and the evidence of efficacy in men had been missing until the post-approval study conducted by Chang et al [38]. It is worth noting that this therapeutic efficacy in men had been predicted by a pharmacodynamic study in which men with IBS had colonic transit responses to alosetron consistent with the efficacy in women [26]. Only recent trials with both alosetron and cilansetron have specifically included men. In summary, both the individual trials, as well as the pooled RR from this meta-analysis indicate effectiveness of 5-HT_3 antagonists in men. It has been suggested that the beneficial effects of 5-HT_3 antagonists on the global IBS symptom complex and IBS related abdominal pain may reflect the beneficial effects on decreasing diarrhea in these patients. However, other effects of this drug class, e.g. on visceral sensation[43] and compliance,[44] indicate additional positive effects responsible for the improvement of IBS symptoms. Moreover, other agents with pure antidiarrheal effects such as loperamide have failed to show beneficial effects on improving IBS related abdominal pain.[45]

In this review, we found a higher risk of constipation in patients receiving 5-HT_3 antagonists, particularly in studies including patients with NC-IBS. Approximately 10 to 43% of the participants who developed constipation withdrew from the trials for this reason. In all of these cases, constipation reportedly resolved rapidly after stopping the treatment. After initial market introduction of alosetron in 2000, there have been reports of serious complications due to constipation in association with alosetron. A recent meta-analysis of clinical trials and post-marketing surveillance data focusing on serious adverse events showed no significant difference in the rate of serious complications of constipation between alosetron- and placebo-using patients[46].

In our meta-analysis, eligible trials have reported 9 cases of at least suspected ischemic colitis in drug-treated patients (estimated incidence 0.2 %) versus none in the comparator group. All cases resolved without sequelae. The recent meta-analysis of clinical trials and post-marketing surveillance data of alosetron reported an incidence of 0.15% with a total of 19 cases of ischemic colitis that all resolved without sequelae. The etiology, pathophysiology and experimental basis for the development of ischemic colitis with this class of compounds remain unclear [47].

Implications for Research and Clinical Policy

This systematic review and meta-analyses aimed to comprehensively assess clinically relevant effects of 5-HT_3 antagonists in NC- and D-IBS and was able to bring to the fore data that up to this point had only been partially reported. For instance, thanks to our inclusion of full text and abstracts, we can infer with some confidence that there is a class effect despite the reporting delays associated with the publication of the 3 cilansetron trials in full (their abstracts were published 2 to 3 years ago). Furthermore, we provide more precise estimates of the risk of constipation and ischemic colitis from these trials. In all, these data, alongside the relative merits of lifestyle behavioral interventions and treatment costs, can help patients and clinicians make informed treatment decisions about the use of these agents for NC- and D-IBS.

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CONCLUSIONS

This systematic review and meta-analysis finds that 5-HT_3 antagonists improve abdominal pain and discomfort, and global IBS symptoms in men and women with non-constipated and diarrhea-predominant IBS. This evidence is consistent across agents within this class and across a broad range of participants in clinical trials. Constipation is a common, but usually mild to moderate side effect of the treatment with 5-HT_3 antagonists. The risk for constipation is lower in patients with predominance of diarrhea and this emphasizes the importance of assessing the individual benefit/risk ratio before starting treatment. Ischemic colitis is a rare adverse event with an incidence of approximately 0.2%. Ischemic colitis and the complications of constipation are still of concern to the regulatory agencies and have led to restriction of this drug class to patients with severe, refractory D-IBS who have failed to respond to conventional treatment.

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Appendix I

Search strategy

The key words were: *serotonin, 5-HT, 5-HT_3 antagonist, alosetron, cilansetron, irritable bowel syndrome, therapy, clinical trial, diarrhea-predominant, and functional bowel disease*.

1 Step: single keywords: alosetron, cilansetron

2. Step: combinations of 2 key words:

- **a.** 5-HT_3 antagonist AND clinical trial, 5-HT_3 antagonist AND irritable bowel syndrome, 5-HT_3 antagonist AND functional bowel disease, 5-HT_3 antagonist AND therapy,
- **b.** alosetron AND clinical trial, alosetron AND irritable bowel syndrome, alosetron AND functional bowel disease, alosetron AND therapy
- **c.** cilansetron AND clinical trial, cilansetron AND irritable bowel syndrome, cilansetron AND functional bowel disease, cilansetron AND therapy

3. Step: combination of 3 key words:

- **a.** 5-HT AND irritable bowel syndrome AND clinical trial, 5-HT AND irritable bowel syndrome AND therapy
- **b.** 5-HT AND functional bowel disease AND clinical trial, 5-HT AND functional bowel disease AND therapy
- **c.** serotonin AND irritable bowel syndrome AND clinical trial, serotonin AND irritable bowel syndrome AND therapy
- **d.** serotonin AND functional bowel disease AND clinical trial, serotonin AND functional bowel disease AND therapy
- **e.** diarrhea-predominant AND irritable bowel syndrome AND clinical trial, diarrhea-predominant AND irritable bowel syndrome AND therapy

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f. diarrhea-predominant AND functional bowel disease AND clinical trial, diarrhea-predominant AND functional bowel disease AND therapy

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Abbreviations used

CI, confidence interval; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine (serotonin); IBS, irritable bowel syndrome; NC, non-constipated; RR, relative risk; RD, Risk difference; NNT, number needed to treat; NNH, number needed to harm.

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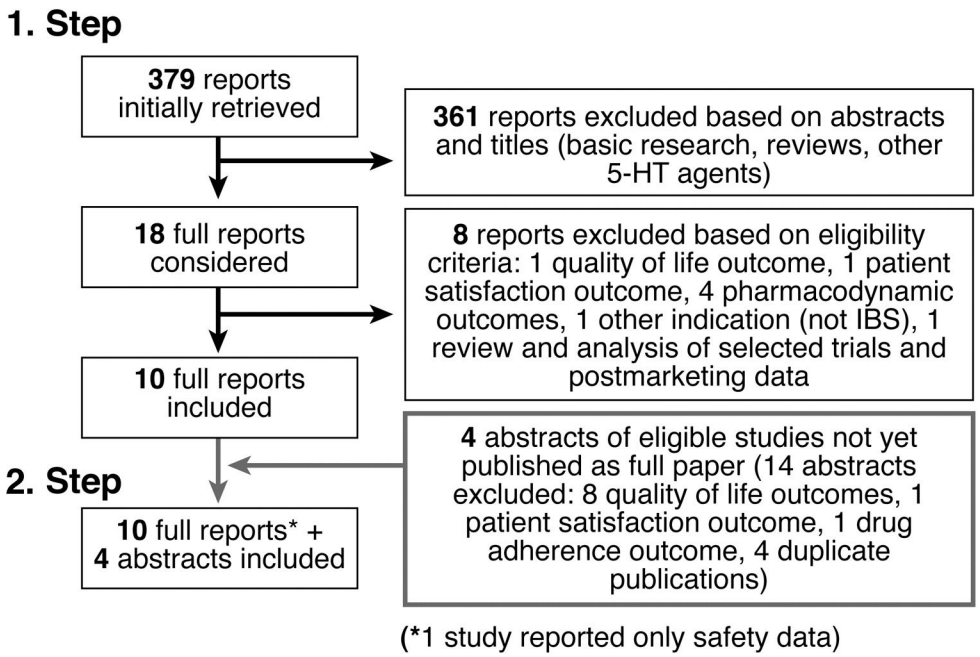

Figure 1.
Trial selection flow

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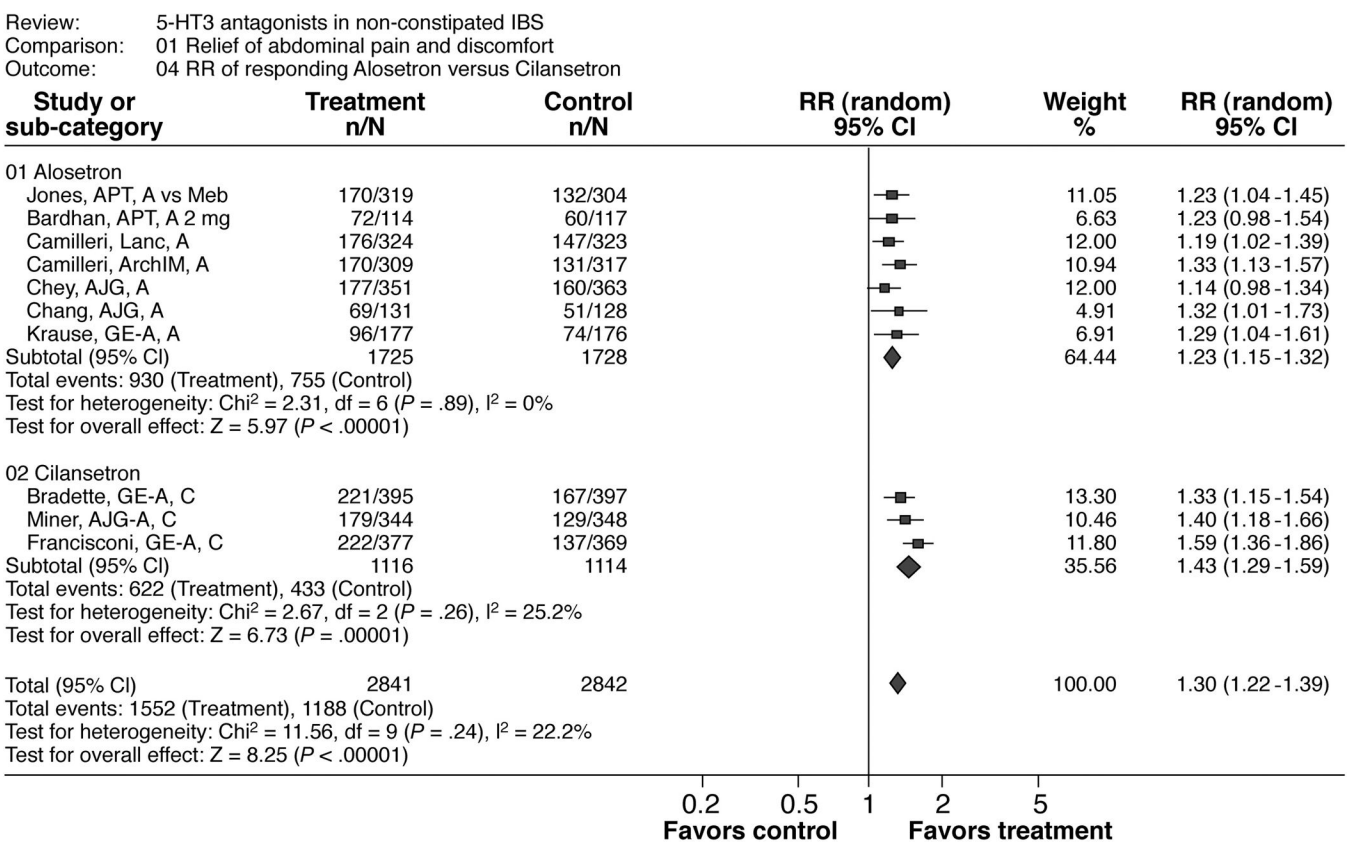

Figure 2.

Patients responding to alosetron or cilansetron regarding “relief of abdominal pain and discomfort”

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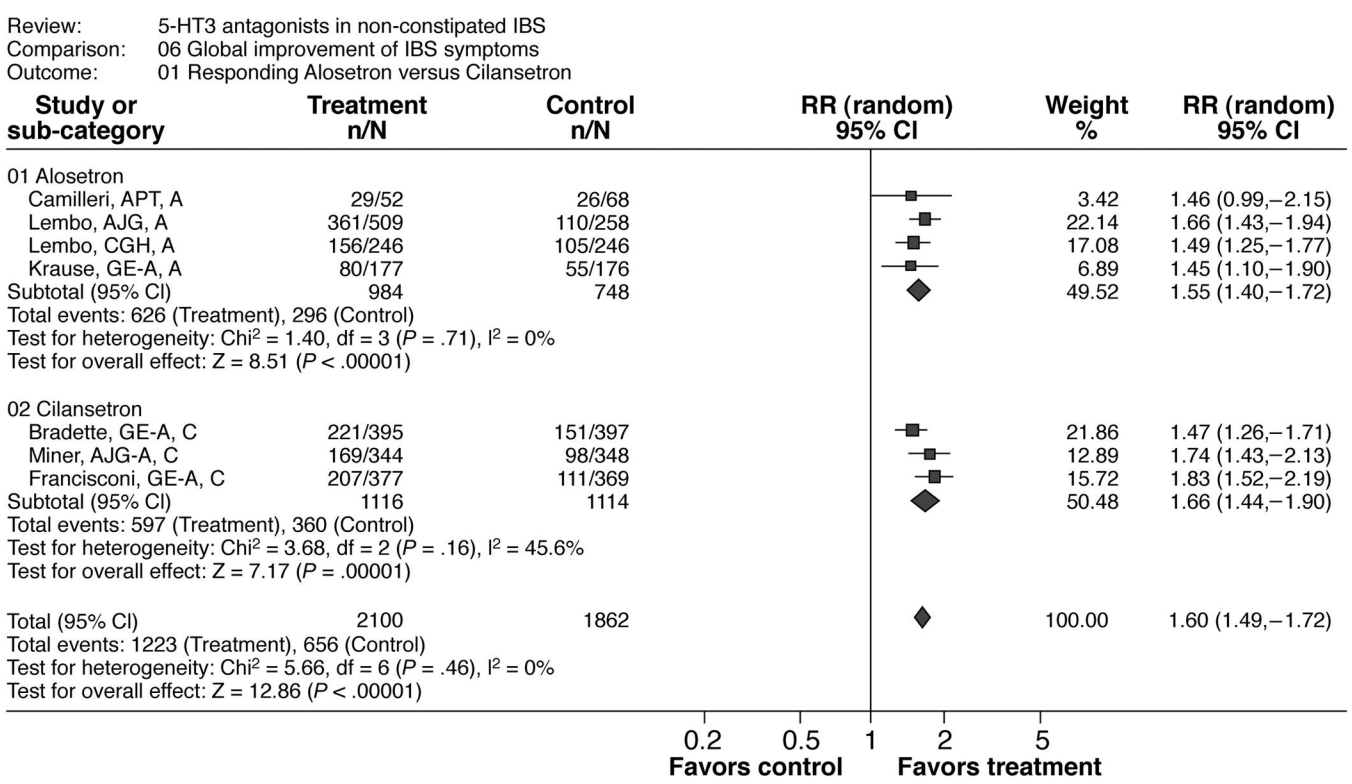

Figure 3.
Patients responding to alosetron or cilansetron regarding “global improvement of IBS symptoms”

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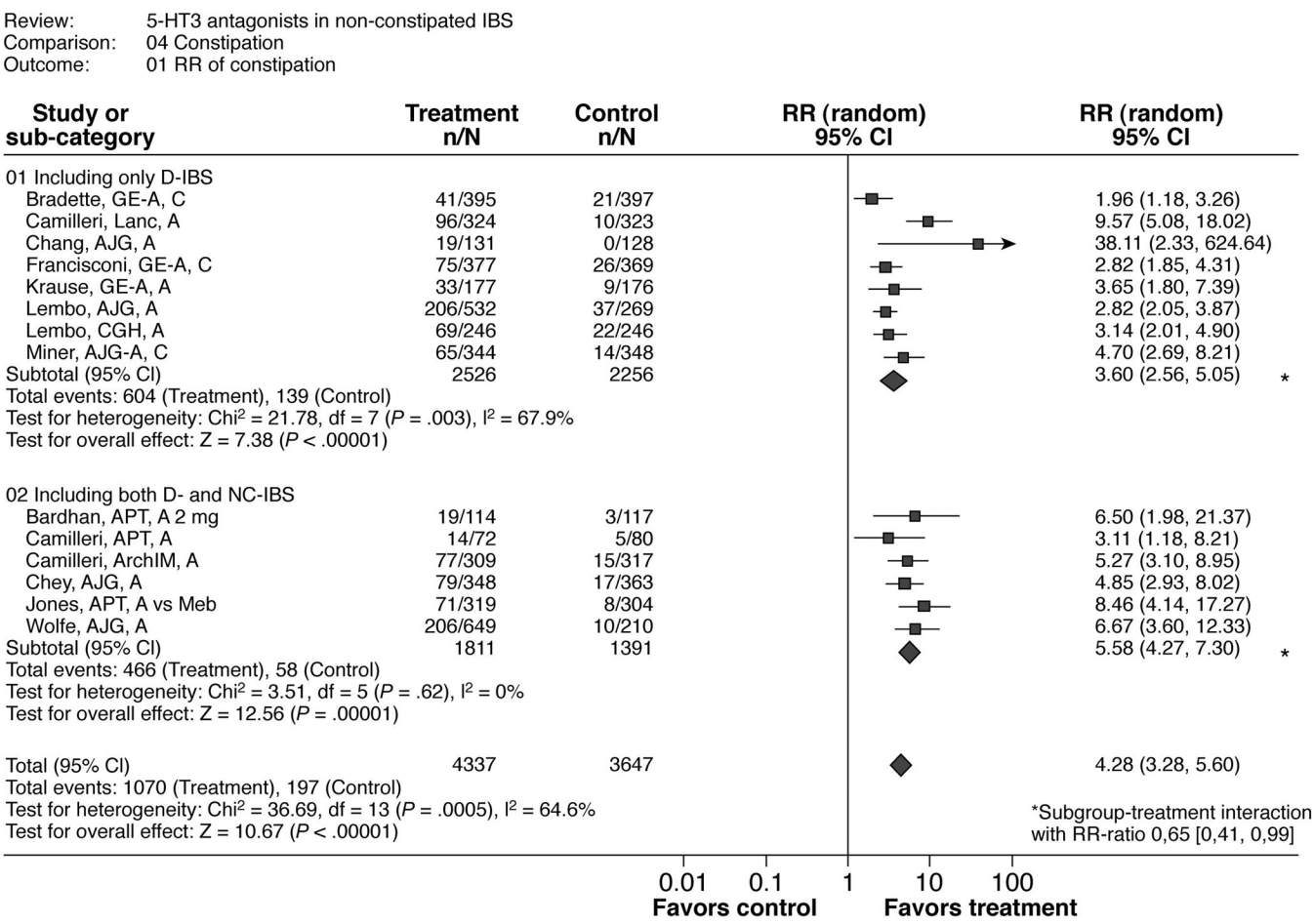

Figure 4.
Number of patients developing constipation

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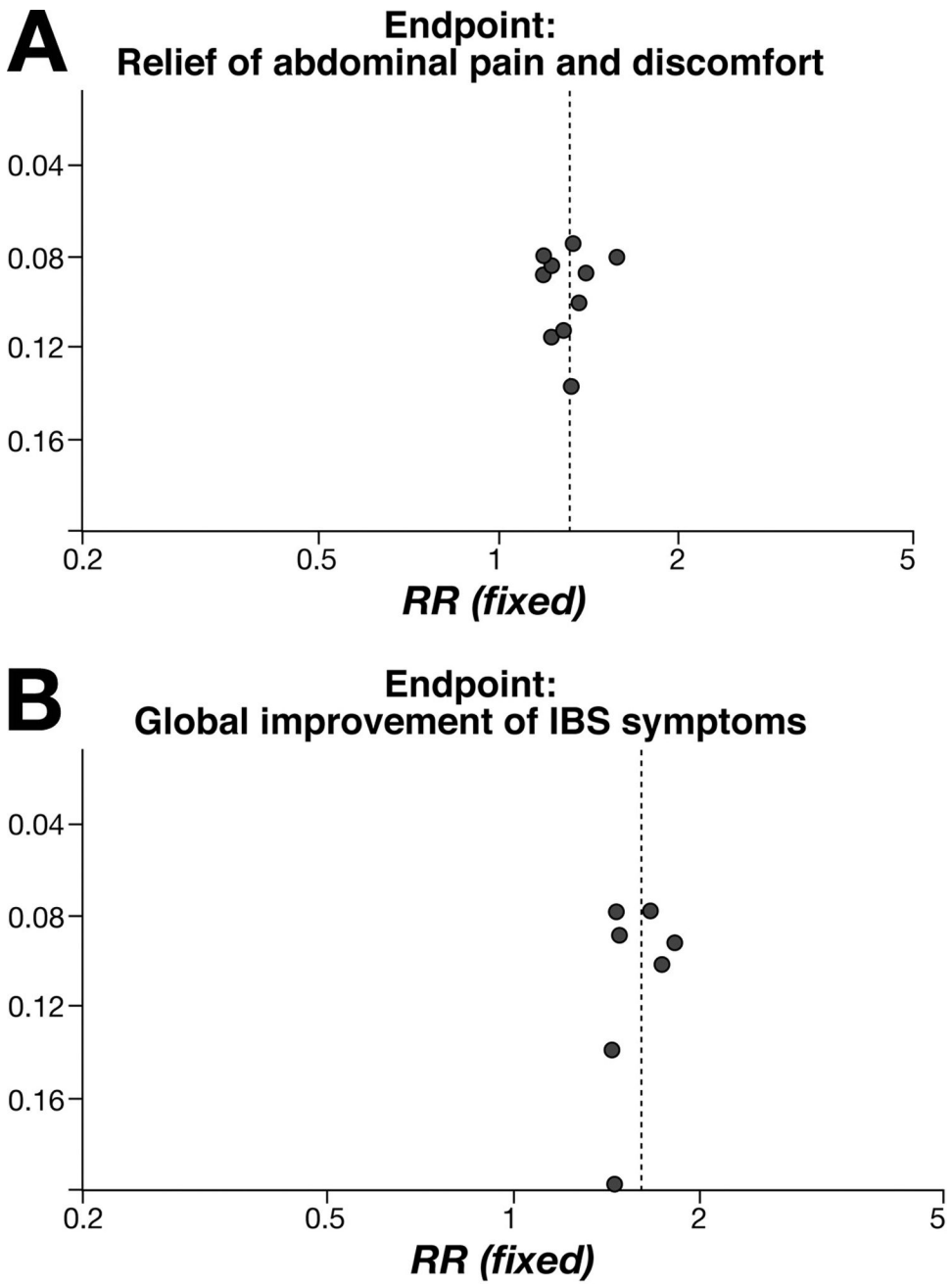

Figure 5.
Funnel plots

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Table 1

Study quality criteria [33] fulfilled by all full paper studies included in the meta-analysis

Validity	Control group Random allocation Masking of patients and investigators Parallel-group design Validated disease definition for inclusion (Rome I and Rome II criteria) Validated outcome measures Attrition bias: to follow up Adequate power for clinically significant effect size Definition of “responder” included a priori Intention to treat analysis
Applicability	Baseline assessment of all treatment groups characteristics Clear description of treatment regimens: dosage, timing, route of administration and duration of treatment Clear definition of outcome and duration of follow up

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Table 2

Details of the studies

Author (year)	Agents	IBS subtype	N	Mean age (SD)	Sex	Dosing[#] (daily)	Treatment duration (weeks)	Efficacy endpoints used	No. (%) lost to follow up
Camilleri (1999)[19]	Alosetron vs. placebo	D-IBS NC-IBS	370	44 (14)	mixed	**2**, 8, 12, 16 mg	12	Global IBS	6 (1.6)
Jones (1999)[20]	Alosetron vs. mebeverine	D-IBS NC-IBS	623	44 (13)	women	**2** mg	12	Abd. Pain	7 (1.1)
Bardhan (2000)[31]	Alosetron vs. placebo	D-IBS NC-IBS	462	43 (14)	mixed	0.2, 1, **4** mg	12	Abd. Pain	8 (1.7)
Camilleri (2000)[29]	Alosetron vs. placebo	D-IBS	647	46 (14)	women	**2** mg	12	Abd. Pain	13 (2)
Camilleri (2001)[30]	Alosetron vs. placebo	D-IBS NC-IBS*	626	46 (13)	women	**2** mg	12	Abd. Pain	17 (2.7)
Lembo (2001)[17]	Alosetron vs. placebo	D-IBS	767	48(13)	women	**2** mg	12	Global IBS	15 (2)
Wolfe (2001)[39]	Alosetron vs. Placebo	D-IBS NC-IBS	869	47 (13)	mixed	**2** mg	48	No efficacy endpoint (safety)	42 (4.8)
Chey (2004)[34]	Alosetron vs. placebo	D-IBS NC-IBS*	714	46	women	**2** mg	48	Abd. Pain	18 (2.5)
Lembo (2004)[32]	Alosetron vs. Placebo	D-IBS	492	49(14)	women	**2** mg	12	Global IBS	15 (3)
Chang (2005)[38]	Alosetron vs. placebo	D-IBS	662	44(13)	men	1, **2,** 4, 8 mg	12	Abd. Pain	19 (2.9)
Minen (A 2004)[21]	Cilansetron vs. placebo	D-IBS	692	n.r.	mixed	**6** mg	12	Abd. Pain Global IBS	n.r.
Bradette (A 2004)[22]	Cilansetron vs. placebo	D-IBS	792	n.r.	mixed	**6** mg	24 (+12 week analysis)	Abd. Pain Global IBS	n.r.
Francisconi (A 2005)[40]	Cilansetron vs. placebo	D-IBS	746	n.r.	mixed	**6** mg	12	Abd. Pain Global IBS	n.r.
Krause (A 2006)[35]	Alosetron vs. Placebo	D-IBS	353	n.r.	women	0.5, 1, **2** mg	12	Abd. Pain Global IBS	n.r.

NC-IBS: IBS with non-constipated bowel habits, D-IBS: diarrhea-predominant IBS

* NC-IBS: Efficacy results were only published for the D-IBS subgroup. This analysis includes the unpublished results for NC-IBS provided by GSK

n.r.= not reported

A= Abstract

patients receiving the dose in bold (i.e. the standard dose of each drug) were included in the final analysis. Sensitivity analysis regarding the Bardhan [31] study, the only one not using the standard dose, did not show a difference between the inclusion of the 4mg vs. the 1 mg group.

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Table 3

Meta-analyses of the beneficial effects of alosetron and cilansetron in patients with IBS with subgroup analysis by agent.

Outcomes Intervention Studies	Treatment group (No. with outcome / Total)	Control group (No. with outcome / Total)	RR (95% CI)	Risk Difference (95% CI)
Relief of abdominal pain and discomfort				
Alosetron				
Jones [20]	170 / 319	132 / 304	1.23 (1.04 1.45)	0.10 (0.02 ,0.18)
Bardhan [31]	72 / 114	60 / 117	1.23 (0.98 1.54)	0.12 (−0.01 ,0.25)
Camilleri [29]	176 / 324	147 / 323	1.19 (1.02 1.39)	0.09 (0.01 ,0.16)
Camilleri [30]	170 / 309	131 / 317	1.33 (1.13 1.57)	0.14 (0.06 ,0.21)
Chey [34]	177 / 351	160 / 363	1.14 (0.98 1.34)	0.06 (−0.01 ,0.14)
Chang [38]	69 / 131	51 / 128	1.32 (1.01 1.73)	0.13 (0.01 ,0.25)
Krause [35]	96 / 177	74 / 176	1.29 (1.04 1.61)	0.12 (0.02 ,0.23)
Random effects RR (I^2 = 0%)			**1.23 (1.15 1.32)**	**0.10 (0.07 ,0.14)**
Cilansetron				
Bradette [22]	221 / 395	167 / 397	1.33 (1.15 ,1.54)	0.14 (0.07 ,0.21)
Miner [21]	177 / 344	129 / 348	1.40 (1.18 ,1.66)	0.15 (0.08 ,0.22)
Francisconi [40]	222 / 377	137 / 369	1.59 (1.36 ,1.86)	0.22 (0.15 ,0.29)
Random effects RR (I^2 = 25%)			**1.43 (1.29 ,1.59)**	**0.17 (0.12 ,0.22)**
Overall pooled effect (I^2 = 22%)			**1.30 (1.22 ,1.39)**	**0.13 (0.10 ,0,16)**
CI = confidence interval; RR = relative risk				
Global improvement of IBS symptoms				
Alosetron				
Camilleri [19]	29 / 52	26 / 68	1.46 (0.99 ,2.15)	0.18 (0.00 ,0.35)
Lembo [17]	361 / 509	110 / 258	1.66 (1.43 ,1.94)	0.28 (0.21 ,0.35)
Lembo [32]	156 / 246	105 / 246	1.49 (1.25 ,1.77)	0.21 (0.12 ,0.29)
Krause [35]	80 / 177	55 / 176	1.45 (1.10 ,1.90)	0.14 (0.04 ,0.24)
Random effects RR (I^2 = 0%)			**1.55 (1.40 ,1.72)**	**0.21 (0.14 ,0.28)**
Cilansetron				
Bradette [22]	221 / 395	151 / 397	1.47 (1.26 ,1.71)	0.18 (0.11 ,0.25)
Miner [21]	169 / 344	98 / 348	1.74 (1.43 ,2.13)	0.21 (0.14 ,0.28)
Francisconi [40]	207 / 377	111 / 369	1.83 (1.52 ,2.19)	0.25 (0.18 ,0.32)
Random effects RR (I^2 = 46%)			**1.66 (1.44 ,1.90)**	**0.21 (0.17 ,0.25)**
Overall pooled effect (I^2 = 22%)			**1.60 (1.49 ,1.72)**	**0.22 (0.18 ,0.25)**

CI = confidence interval

IBS = irritable bowel syndrome

RR = relative risk

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Table 4

Meta-analysis of the effect of alosetron and cilansetron on constipation, results by patient subgroup.

Patient type Studies	Treatment group (No. with constipation / Total)	Control group (No. with constipation / Total)	RR (95% CI)	Risk Difference (95% CI)
Only D-IBS				
Bradette [22]	41 / 395	21 / 397	1.96 (1.18, 3.26)	0.05 (0.01, 0.09)
Camilleri [29]	96 / 324	10 / 323	9.57 (5.08, 18.02)	0.27 (0.21, 0.32)
Chang [38]	19 / 131	0 / 128	38.1 (2.33, 624.6)	0.15 (0.08, 0.21)
Francisconi [40]	75 / 377	26 / 369	2.82 (1.85, 4.31)	0.13 (0.08, 0.18)
Krause [35]	33 / 177	9 / 176	3.65 (1.80, 7.39)	0.14 (0.07, 0.2)
Lembo [17]	206 / 532	37 / 269	2.82 (2.05, 3.87)	0.25 (0.19, 0.31)
Lembo [32]	69 / 246	22 / 246	3.14 (2.01, 4.90)	0.19 (0.12, 0.26)
Miner [21]	65 / 344	14 / 348	4.70 (2.69, 8.21)	0.15 (0.10, 0.19)
Random effects RR (I^2 = 68%)			**3.60 (2.56, 5.05)**	**0.16 (0.11, 0.22)**
D-IBS and NC-IBS				
Bardhan [31]	19 / 114	3 / 117	6.50 (1.98, 21.4)	0.14 (0.07, 0.22)
Camilleri [19]	14 / 72	5 / 80	3.11 (1.18, 8.21)	0.13 (0.03, 0.24)
Camilleri [30]	77 / 309	15 / 317	5.27 (3.10, 8.95)	0.2 (0.15, 0.26)
Chev [34]	79 / 348	17 / 363	4.85 (2.93, 8.02)	0.18 (0.13, 0.23)
Jones [20]	71 / 319	8 / 304	8.46 (4.14, 17.3)	0.2 (0.15, 0.25)
Wolfe [39]	206 / 649	10 / 210	6.67 (3.60, 12.3)	0.27 (0.22, 0.32)
Random effects RR (I^2 = 0%)			**5.58 (4.27, 7.30)**	**0.2 (0.16, 0.23)**
Overall pooled effect (I^2 = 65%)			**4.28 (3.28, 5.60)**	**0.17 (0.14, 0.21)**

CI = confidence interval

D-IBS = diarrhea-predominant irritable bowel syndrom

NC-IBS = non-constipated irritable bowel syndrome

RR = relative risk

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Table 5

Subgroup analyses for the efficacy endpoints

a) Endpoint: relief of abdominal pain and discomfort

Subgroups	Subgroup 1 (No of studies) RR [95%CI]	Subgroup 2 (No of studies) RR [95%CI]	Test of Interaction RR-Ratio [95%CI]
Drugs	Alosetron (7) 1.23 [1.15, 1.32]	Cilansetron (3) 1.43 [1.29, 1.59]	**0.86 [0.76, 0.98]**
Endpoint definition	Yes/No response (9) 1.31 [1.22, 1.40]	Responder cut-off: 10% change in pain severity (1) 1.23 [0.98, 1.54]	1.07 [0.84, 1.35]
Endpoint assessment	Reported average (6) 1.34 [1.21, 1.47]	Calculated average (4) 1.25 [1.15, 1.37]	1.07 [0.94, 1.22]
Gender	Only female (5) 1.23 [1.14, 1.32]	Mixed gender (5) 1.39 [1.28, 1.51]	**0.88 [0.79, 0.99]**
Treatment duration	12 weeks (8) 1.33 [1.23, 1.42]	24/48 weeks (2) 1.24 [1.07, 1.44]	1.07 [0.91, 1.27]
Study population	Mixed NC- and D-IBS (2) 1.23 [1.13, 1.34]	D-IBS only (8) 1.35 [1.24, 1.47]	0.91 [0.81, 1.03]
Publication Type	Full Paper (6) 1.23 [1.14, 1.32]	Abstract only (4) 1.41 [1.29, 1.54]	**0.87 [0.78, 0.98]**

b) Endpoint: global improvement of IBS symptoms

Subgroups	Subgroup 1 (No of studies) RR [95%CI]	Subgroup 2 (No of studies) RR [95%CI]	Test of Interaction RR-Ratio [95%CI)]
Drugs	Alosetron (4) 1.55 [1.40, 1.72]	Cilansetron (3) 1.66 [1.44, 1.90]	0.93 [0.79, 1.11]
Endpoint definition	Yes/No response (5) 1.61 [1.45, 1.78]	Responder cut-off: at least moderately improved (2) 1.58 [1.41, 1.78]	1.02 [0.87, 1.19]
Endpoint assessment	Reported average (3) 1.66 [1.44, 1.90]	Calculated average (4) 1.55 [1.40, 1.72]	1.07 [0.90, 1.27]
Gender	Only female (3) 1.56 [1.41, 1.74]	Mixed gender (4) 1.64 [1.46, 1.84]	0.95 [0.81, 1.11]
Treatment duration	12 weeks (6) 1.64 [1.51, 1.77]	24 weeks (1) 1.33 [1.16, 1.52]	**1.23 [1.05, 1.44]**
Study population	Mixed NC- and D-IBS (1) 1.46 [0.99,2.15]	D-IBS only (6) 1.60 [1.49, 1.73]	0.91 [0.61, 1.35]
Publication Type	Full Paper (3) 1.57 [1.41, 1.76]	Abstract (4) 1.62[1.44, 1.82]	0.97 [0.83, 1.14]

CI = confidence interval

D-IBS = diarrhea-predominant irritable bowel syndrome

NC-IBS = non-constipated irritable bowel syndrome

RR = relative risk

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Table 6

Subgroup analyses for constipation

Subgroups	Subgroup 1 (No of studies) RR [95%CI]	Subgroup 2 (No of studies) RR [95%CI)]	Test of Interaction RR-Ration [95%CI)]
Drugs	Alosetron (11) 4.89 [3.6, 6.56]	Cilansetron (3) 2.92 [1.85, 4.63]	1.68 [0.96, 2.91]
Gender	Only female (8) 4.85 [3.48, 6.76]	Mixed gender (6) 3.39 [2.19, 5.24]	1.43 [0.85, 2.41]
Treatment duration	12 weeks (11) 4.40 [3.27, 5.92]	24/48 weeks (3) 3.94 [1.89, 8.23]	1.12 [0.51, 2.47]
Study population	D-IBS only (8) 3.6 [2.56, 5.05]	Mixed NC- and D-IBS (6) 5.58 [4.27, 7.30]	**0.65 [0.41, 0.99]**
Publication Type	Abstract only (4) 3.03 [2.11, 4.37]	Full Paper (10) 5.07 [3.62, 7.09]	**0.60 [0.36, 0.98]**