ORIGINAL ARTICLE

AG-2017-127
dx.doi.org/10.1590/S0004-2803.201800000-41

Efficacy and safety of intestinal secretagogues for chronic constipation: a systematic review and meta-analysis

Juan Sebastian **LASA**, María Josefina **ALTAMIRANO**, Luis Florez **BRACHO**, Silvina **PAZ** and Ignacio **ZUBIAURRE**

Received 23/12/2017
Accepted 19/2/2018

ABSTRACT – **Background** – Intestinal secretagogues have been tested for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. The class-effect of these type of drugs has not been studied. **Objective** – To determine the efficacy and safety of intestinal secretagogues for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. **Methods** – A computer-based search of papers from 1966 to September 2017 was performed. Search strategy consisted of the following MESH terms: intestinal secretagogues OR linaclotide OR lubiprostone OR plecanatide OR tenapanor OR chloride channel AND chronic constipation OR irritable bowel syndrome. Data were extracted as intention-to-treat analyses. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as Relative Risk of achieving an improvement in the symptom under consideration. **Results** – Database Search yielded 520 bibliographic citations: 16 trials were included for analysis, which enrolled 7658 patients. Twelve trials assessed the efficacy of intestinal secretagogues for chronic constipation. These were better than placebo at achieving an increase in the number of complete spontaneous bowel movements per week [RR 1.87 (1.24-2.83)], at achieving three or more spontaneous bowel movements per week [RR 1.56 (1.31-1.85)] and at inducing spontaneous bowel movement after medication intake [RR 1.49 (1.07-2.06)]. Similar results were observed when assessing the efficacy of intestinal secretagogues on constipation-predominant irritable bowel syndrome based on the results of six trials. **Conclusion** – Intestinal secretagogues are useful and safe therapeutic alternatives for the treatment of constipation-related syndromes.

HEADINGS – Constipation. Irritable bowel syndrome. Colon.

INTRODUCTION

Chronic constipation (CC) as well as constipation-predominant irritable bowel syndrome (IBS-C) are very common conditions that constitute a frequent reason for referral to the general practitioner and the gastroenterology specialist[1]. These conditions are associated with a significant morbidity and an impaired quality of life[2].

Even though they are classified as different entities according to Rome criteria[3], the physiological mechanisms behind CC and IBS-C share a common ground. Thus, a diminished contractile activity of the colonic muscular layer as well as alterations in water reabsorption or secretion through intestinal epithelium have been proposed as etiological mechanisms[4]. As a consequence, they have been regarded as potential targets for pharmacological therapy.

Conventional treatment for CC and IBS-C include changes in lifestyle, increase of fiber intake and the use of a myriad of laxatives[5]. It can also contemplate other therapies oriented to treat constipation-related symptoms, such as abdominal bloating or pain[6]. It is noteworthy that a significant proportion of patients will not experience an improvement with these measures. Over the last years, new therapeutic alternatives have been developed: new high-affinity 5-HT4 receptor agonists such as prucalopride have been successfully tested; however, previous experience with similar molecules may raise a concern regarding their safety[7].

Among these new alternatives, intestinal secretagogues have shown some promising results. These drugs are designed to increase intestinal fluid secretion, thus increasing bowel movement frequency as well as enhancing the amount of stool water[8]. These molecules can act at different points: linaclotide for instance is a guanylate cyclase-C agonist that activates the cystic fibrosis transmembrane conductance regulator in the intestinal epithelium[9], whereas lubiprostone activates type 2 Chloride channels in the aforementioned cells[10]. The common pathway of these mechanisms is an increased release of chloride – and water – to the intestinal lumen.

These drugs have now been tested in different clinical settings for the treatment of both CC and IBS-C, and the preliminary results have triggered the development of drugs with similar mechanism of action, such as plecanatide or tenapanor[11]. The class-effect of these type of drugs has not been extensively studied. As a consequence, we sought to determine the efficacy and safety of intestinal secretagogues for the treatment of CC and IBS-C.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Gastroenterology Department. Hospital Britanico de Buenos Aires. Buenos Aires, Argentina.
Corresponding author: Juan Sebastian Lasa. E-mail: juanselasa@gmail.com

METHODS

Search strategy and study selection

A computer-based search of compatible papers from 1966 to November 2017 was performed using the following databases: MEDLINE-Pubmed, EMBASE, LILACS and The Cochrane Library. Search strategy consisted of the following MeSH terms: intestinal secretagogues OR linaclotide OR lubiprostone OR plecanatide OR tenapanor OR chloride channel AND chronic constipation OR irritable bowel syndrome.

Relevant paper's bibliographies were revised, as well as bibliographies from previously published meta-analyses. A manual search for potentially relevant abstracts from Digestive Disease Week and United European Gastroenterology Week from 2009-2017 was also undertaken.

Two authors performed bibliographic search in an independent manner. Potentially relevant abstracts were revised in order to check its inclusion. Inclusion criteria were: a) trials examining the efficacy of any intestinal secretagogue for CC and/or IBS-C treatment; b) randomized, placebo-controlled trials; c) trials performed on adults. There were no language restrictions.

Search findings were then compared. If there was disagreement on the inclusion of a particular trial, it was discussed and determined by consensus. If there was evidence of duplication of data, the main author would be contacted to determine its inclusion.

Methodological evaluation of included studies

Methodological assessment was done using the *Evidence-Based Gastroenterology Steering Group* recommendations[12]. A Jadad score of each trial was also calculated. If a significant difference in methodological quality among studies was observed, a sensitivity analysis would be undertaken by excluding those trials with less quality. If relevant data was missing in original manuscripts, authors would be contacted.

Outcome measures

The following outcomes were considered for analysis: three or more spontaneous bowel movements (SBM) per week, number of complete spontaneous bowel movements (CSBM) per week, SBM after medication administration, improvement in abdominal pain, global relief of symptoms. Since Rome IV criteria[3] disregard abdominal discomfort as a pivotal symptom for the definition of IBS, we decided that it should not be contemplated as an endpoint, even though most trials assessed this point in particular. Data were extracted as intention-to-treat analyses, in which all dropouts are assumed to be treatment failures, wherever trial reporting allowed this.

Statistical analysis

Meta-analysis was performed using REVMAN software (Review Manager Version 5.2. Copenhagen: The Nordic Cochrane Collaboration, 2012). Heterogeneity among studies was evaluated by means of chi square and I2 tests. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as relative risk (RR) of achieving an improvement in the symptom under consideration. Also, 95% confidence intervals were calculated. Funnel plots were designed to evaluate possible publication bias. Numbers necessary to treat (NNT) were calculated.

RESULTS

Database Search yielded 520 bibliographic citations, as shown in FIGURE 1. Of these, 18 full texts were assessed for eligibility and 16 trials were finally included for analysis[13-27], which enrolled 7658 patients.

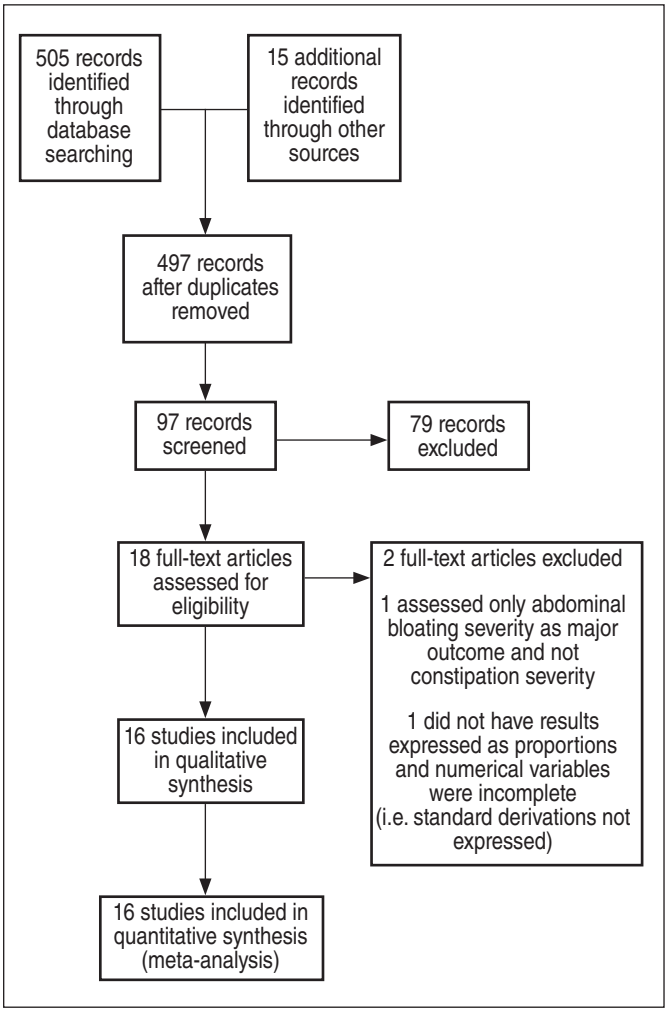

FIGURE 1. Flow chart showing the results of the bibliographic search and final selection of inc luded studies.

The main characteristics of included trials are described in TABLE 1. One of the most challenging aspects of this systematic review was the heterogeneity in the assessment of experimental drugs efficacy: as a consequence, not every trial was included in the assessment of each of the endpoints considered for meta-analysis. Patients were not similar: from an etiologic point of view, we divided trials evaluating the efficacy and safety of intestinal secretagogues on patients with CC and with IBS-C. Furthermore, CC patients also included patients with opioid-induced constipation as well as constipation associated with Parkinson disease[21] and diabetes mellitus[25].

Methodological evaluation of included trials is described in TABLE 2. No trial was excluded due to methodological limitations. No significant publication bias was found according to the Egger test (P>0.5).

TABLE 1. Main characteristics of included studies.

Author (Year)	Countrie	Age (median), Gender (%F) and Diagnosis	Outcome Measures	Number of Patients	Interventions	Co-Interventions
LINACLOTIDE						
Johnston 2010	USA/ Canada	44.4/92%; CIC+IBS-C	% of patients with CBM; % of patients with >3 BM during 75% of treatment period; % of patients with Bristol Score >3; % of patients without significant constipation; abdominal pain severity; abdominal bloating severity; % of patients with global relief	85 patients on placebo; 79 on linaclotide 75 ug; 82 on linaclotide 150 ug; 84 on linaclotide 300 ug; 89 on linaclotide 600 ug	Linaclotide once per day or placebo for 12 weeks	Bisacodyl or phosphate enema as rescue medication
Lembo 2010	USA	47.3/92%/ CIC	% of patients with CBM; % of patients with SBM; % of patients with Bristol Score>3; % of patients without significant straining; abdominal pain and bloating severity; % of patients with global relief	68 patients on placebo; 59 on linaclotide 75 ug; 56 on linaclotide 150 ug; 62 on linaclotide 600 ug	Oral linaclotide once daily or placebo for 4 weeks	Bisacodyl or phosphate enema as rescue medication
Lembo 2011	USA and Canada (2 clinical trials)	47.8/89.7%/ CIC	% of patients with >3 CSBM in 9 out of 12 weeks and/or increase in >1/week; % of patients with SBM after medication intake; % of patients with >2 SBM/week; % of patients with global relief	424 patients on placebo; 430 on linaclotide 145 ucg; 418 on linaclotide 290 ucg	Linaclotide or placebo for 12 weeks	Not clear
Chey 2012	USA	44.3/ 89.55%/ IBS-C	% of patients with pain severity improvement of >30% for at least 6 out of 12 weeks; % of patients with >1 CSBM/week for at least 6 out of 12 weeks; % of patients with >3 CBM/week; % of patients with CSBM after medication intake; % of patients with >2 SBM/week; % of patients with Bristol Score>3; % of patients with global relief	403 patients on placebo; 402 on linaclotide 290 ucg	Linaclotide or placebo for 26 weeks (assessment after 12 weeks of completion)	Not clear
Rao 2012	USA and Canada	43.5/90.5%/ IBS-C	% of patients with pain severity improvement >30% for at least 6 out of 12 weeks; % of patients with >1 CSBM/week for 6 out of 12 weeks; % of patients with >3 CBM/week; % of patients with SBM after medication intake; % of patients >2 SBM/week; % of patients with Bristol Score >3; % of patients with global relief	395 patients on placebo; 405 patients on linaclotide 290 ucg	Linaclotide or placebo for 12 weeks	Oral or rectal bisacodyl as rescue treatment
LUBIPROSTONE						
Johanson 2008	USA	48.27/90.55%/ CIC	% of patients with SBM; straining severity score; Bristol score; bloating and abdominal discomfort severity; % of patients who required rescue treatment	33 patients on placebo; 30 on lubiprostone 24 mcg; 32 on lubiprostone 48 mcg; 34 on lubiprostone 72 mcg	Lubiprostone or placebo T.I.D. for 3 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Drossman 2008	USA	46.6/91.6%/ IBS-C	% of patients with global improvement of IBS symptom severity: SBM, abdominal pain and bloating	385 patients on placebo; 769 on lubiprostone 8 mcg	Lubiprostone or placebo T.ID. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Fukudo 2011	Japan	39.4/90.58%/ CIC+IBS-C	P% of patients with SBM after medication intake; % of patients with global relief	42 patients on placebo; 41 on lubiprostone16 mcg; 43 on lubiprostone 32 mcg; 44 on lubiprostone 48 mcg	Lubiprostone or placebo for 2 weeks	Bisacodyl suppositories or glycerol enema as rescue treatment
Ondo 2012	USA	67.3/24.59%/ Constipation on Parkinson patients	% of patients with global relief; number of SBM/week with medication	31 patients on placebo; 30 on lubiprotsone 24 mcg	Lubiprostone or placebo B.I.D. for 4 weeks	Not clear
Cryer 2014	USA and Canada	50.4/64.35%/ opiod-induced constipation	% of patients with SBM after medication intake; % of patients with >3 SBM/week for at least 50% of treatment duration	208 patients on placebo; 210 patients on lubiprostone 24 mcg	Lubiprostone or placebo B.I.D. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Fukudo 2015	Japan	42.1/87.9%/ CIC	% of patients with SBM after medication intake; % of patients with >4 SBM/week; constipation severity	62 patients on placebo; 62 patients on lubiprostone 48 mcg	Lubiprostone or placebo for 4 weeks	Bisacodyl suppositories or glycerol enema as rescue treatment

Jamal 2015	USA and Europe	51.7/63.11%/ opioid-induced constipation	% of patients with SBM after medication intake	217 patients on placebo; 214 on lubiprostone 24 mcg BID	Lubiprostone or placebo B.I.D. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Christie 2017	USA	56.7/65.5%/ constipation on diabetic patients	% of patients with CSBM; average number of SBM/week	39 patients on placebo / 37 patients on lubiprostone 24 mcg BID	Lubiprostone or placebo B.I.D. for 8 weeks	Laxatives (including PEG) as rescue treatment
PLECANATIDE						
Miner 2017	USA and Canada	45.4/80.75%/ CIC	% of patients with >3 CSBM and/or increase in SBM/week in 9 out of 12 weeks of treatment; % of patients with SBM after medication intake	452 patients on placebo; 452 on plecanatide 3 mg; 441 on plecanatide 6 mg	Plecanatide or placebo once daily for 12 weeks	Bisacodyl as rescue treatment
TENAPANOR						
Chey 2017	USA	45.7/ 86.8%/ IBS-C	% of patients with >SBM/week for at least 50% of the treatment duration; % of patients with >30% decrease of abdominal pain severity for at least 50% of the treatment duration	89 patients on placebo; 85 on tenapanor 5 mg; 87 on tenapanor 20 mg; 84 on tenapanor 50 mg BID	Tenapanor or placebo B.I.D. for 12 weeks	Bisacodyl or suppositories as rescue treatment

CIC: chronic idiopathic constipation; IBS-C: constipation-predominant irritable bowel syndrome; CBM: complete bowel movement; SBM: spontaneous bowel movement; CSBM: complete spontaneous bowel movement; B.I.D: bis in die.

TABLE 2. Methodological features of included studies.

Study ID	Concealed allocation	Blinding of patients and healthcare personnel	Equalco-interventions between groups	Follow up report	Intention to treat analysis	Jadad score
LINACLOTIDE						
Johnston 2010	Yes	Yes	Yes	Yes	Yes	7
Lembo 2010	Yes	Yes	Yes	Yes	Yes	7
Lembo 2011	Yes	Yes	Yes	Yes	Yes	7
Chey 2012	Yes	Yes	Yes	Yes	Yes	7
Rao 2012	Yes	Yes	Yes	Yes	Yes	7
LUBIPROSTONA						
Johanson 2007	Not clear	Yes	Yes	Yes	Yes	6
Drossman 2008	Not clear	Yes	Yes	Yes	Yes	6
Fukudo 2010	Not clear	Yes	Yes	Yes	No	6
Ondo 2012	Yes	Yes	Yes	Yes	No	6
Cryer 2014	Yes	Yes	Yes	Yes	Yes	7
Fukudo 2014	Not clear	Yes	Yes	Yes	No	6
Jamal 2015	Yes	Yes	Yes	Yes	Yes	7
Christie 2017	Not clear	Yes	Yes	Yes	Not clear	6
PLECANATIDE						
Miner 2017	Yes	Yes	Yes	Yes	Yes	7
TENAPANOR						
Chey 2017	Yes	Yes	Yes	Yes	Yes	7

Efficacy of intestinal secretagogues for patients with chronic constipation

Twelve randomized controlled trials assessed the efficacy of three drugs for CC patients: linaclotide (Johnston 2010, Lembo 2010 and the two controlled trials published in Lembo 2011), lubiprostone (Johanson 2007, Fukudo 2011, Ondo 2012, Cryer 2014, Fukudo 2015, Jamal 2015 and Christie 2017) and plecanatide (Miner 2017). Efficacy endpoints are described in FIGURE 2. Overall, intestinal secretagogues were better than placebo at achieving an increase in the number of CSBM per week [RR 1.87 (1.24-2.83), NNT 9], also at achieving three or more SBM per week [RR 1.56 (1.31-1.85), NNT 6] and at inducing SBM after medication intake [RR 1.49 (1.07-2.06), NNT 6]. Additionally, patients treated with intestinal secretagogues experienced a more significant global relief of their symptoms compared to placebo [RR 1.78 (1.18-2.69), NNT 7]. In the cases where a significant heterogeneity was found, a sensitivity analysis was performed, showing no significant changes.

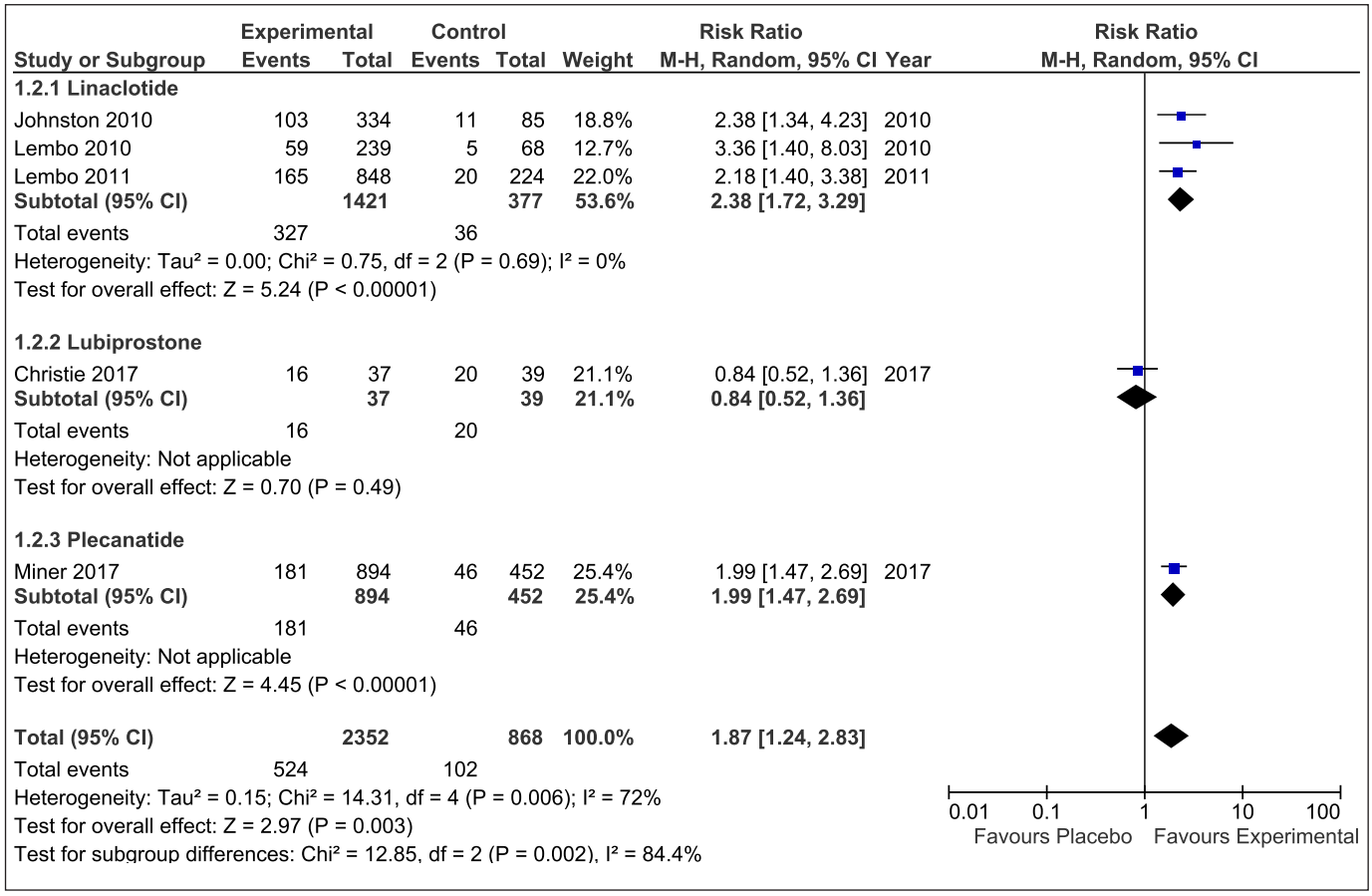

FIGURE 2. Efficacy of intestinal secretagogues on chronic idiopathic constipation patients, based on the following endpoints: A) Increase in the number of CSBM per week.

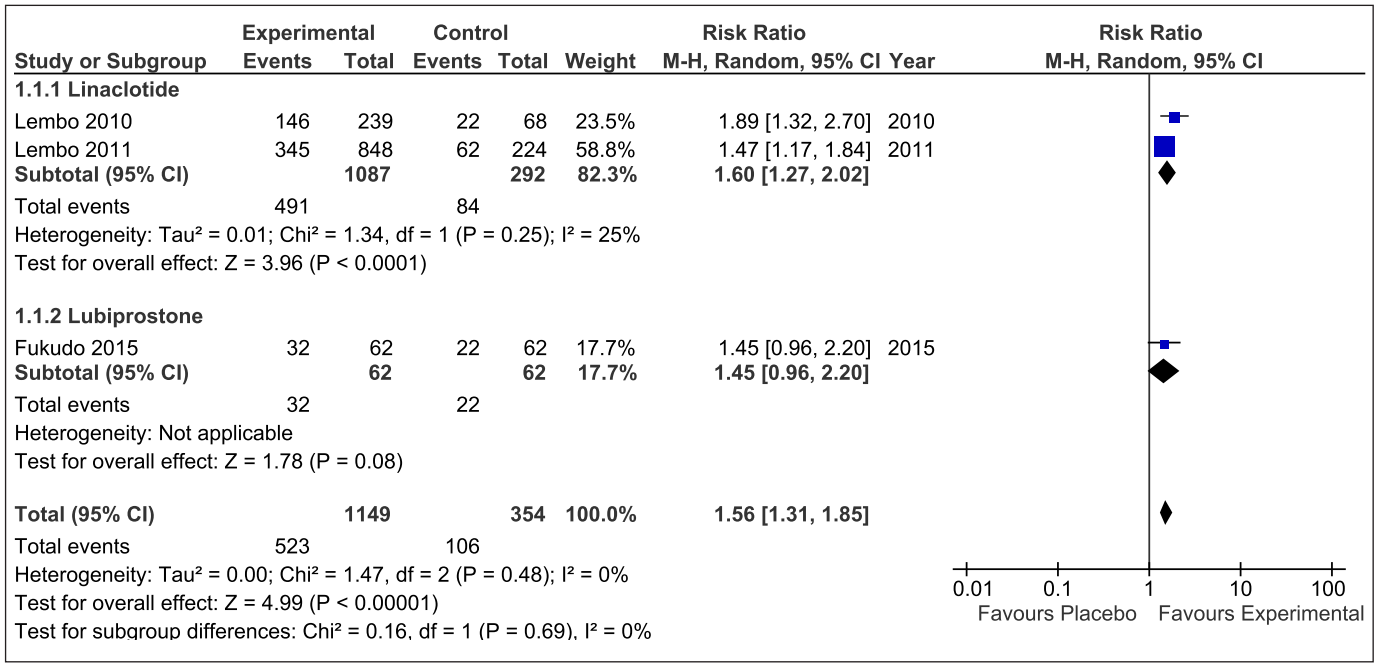

FIGURE 2. B) Achievement of >3 SBM per week.

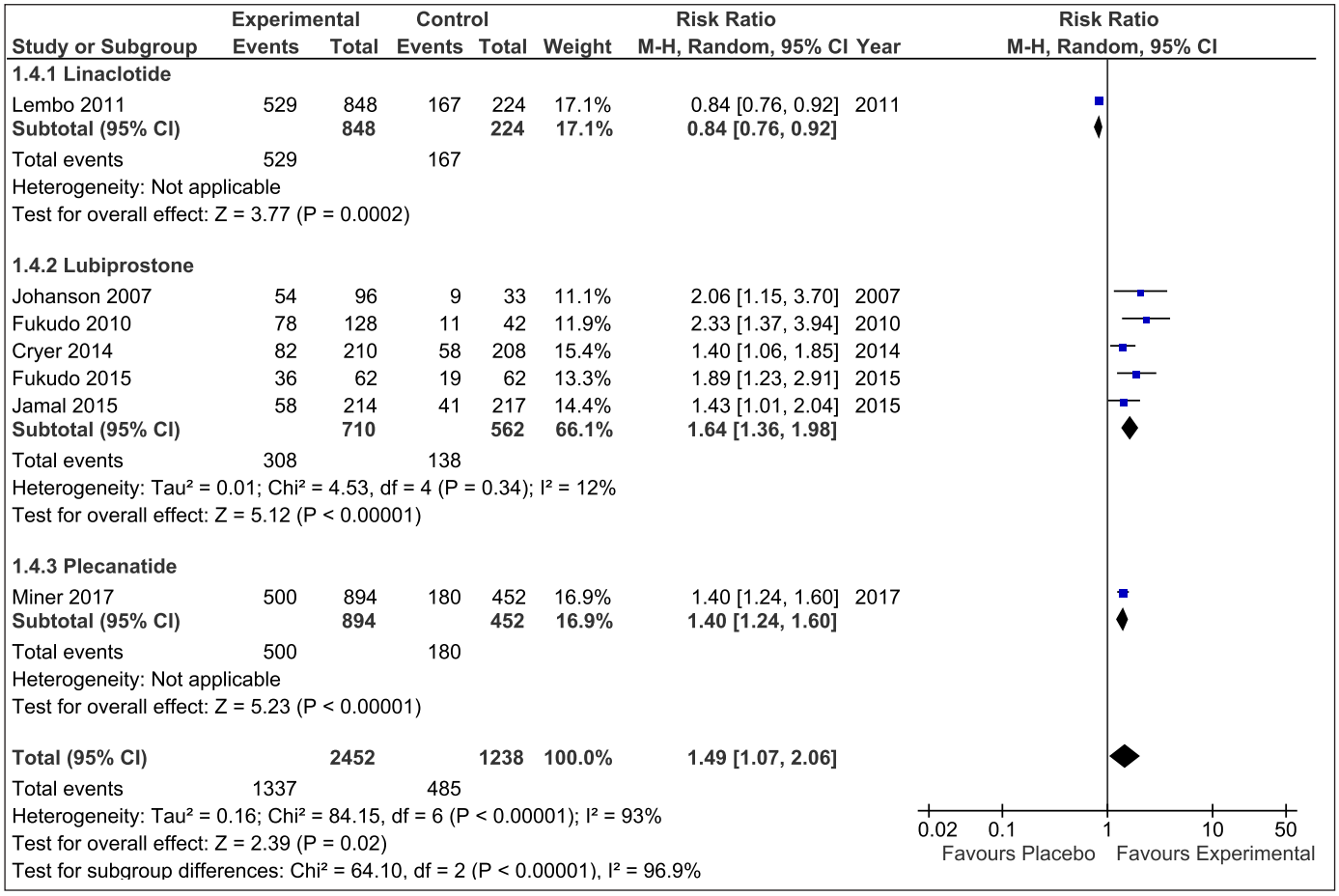

FIGURE 2. C) SBM after medication intake.

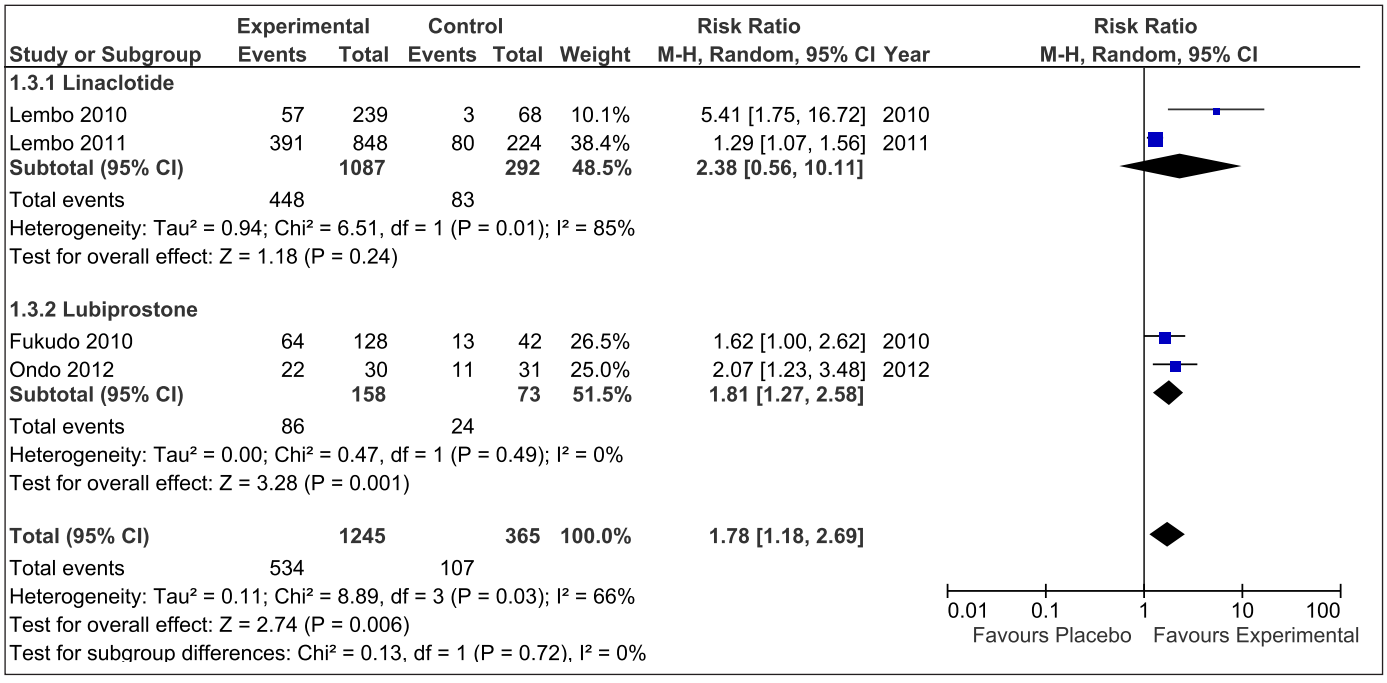

FIGURE 2. D) Achievement of global relief.

Efficacy of intestinal secretagogues for patients with constipation-predominant irritable bowel syndrome

Six randomized controlled trials assessed the efficacy of three drugs for IBS-C patients: linaclotide (Johnston 2010, Rao 2012, Chey 2012), lubiprostone (Fukudo 2011, Drossmann 2009) and tenapanor (Chey 2017). Efficacy endpoints are described in FIGURE 3. Intestinal secretagogues were not only better at achieving a relief in constipation-related outcomes such as increase in CSBM [RR 2.44 (1.51-3.93), NNT 5], three or more SBM per week [RR 1.97 (1.74-2.24), NNT 3], SBM after medication intake [RR 1.60 (1.44-1.79), NNT 4], but also a significant improvement in abdominal pain was observed versus placebo [RR 1.34 (1.21-1.48), NNT 9]. In the cases where a significant heterogeneity was found, a sensitivity analysis was performed, showing no significant changes.

Adverse events

A pooled analysis of the most frequent adverse events is detailed in TABLE 3. Overall, intestinal secretagogues showed to be safe drugs, without a significant proportion of serious adverse events reported. By far, the most common adverse event – which caused drop outs throughout most of the included studies – was diarrhea along with abdominal pain and nausea.

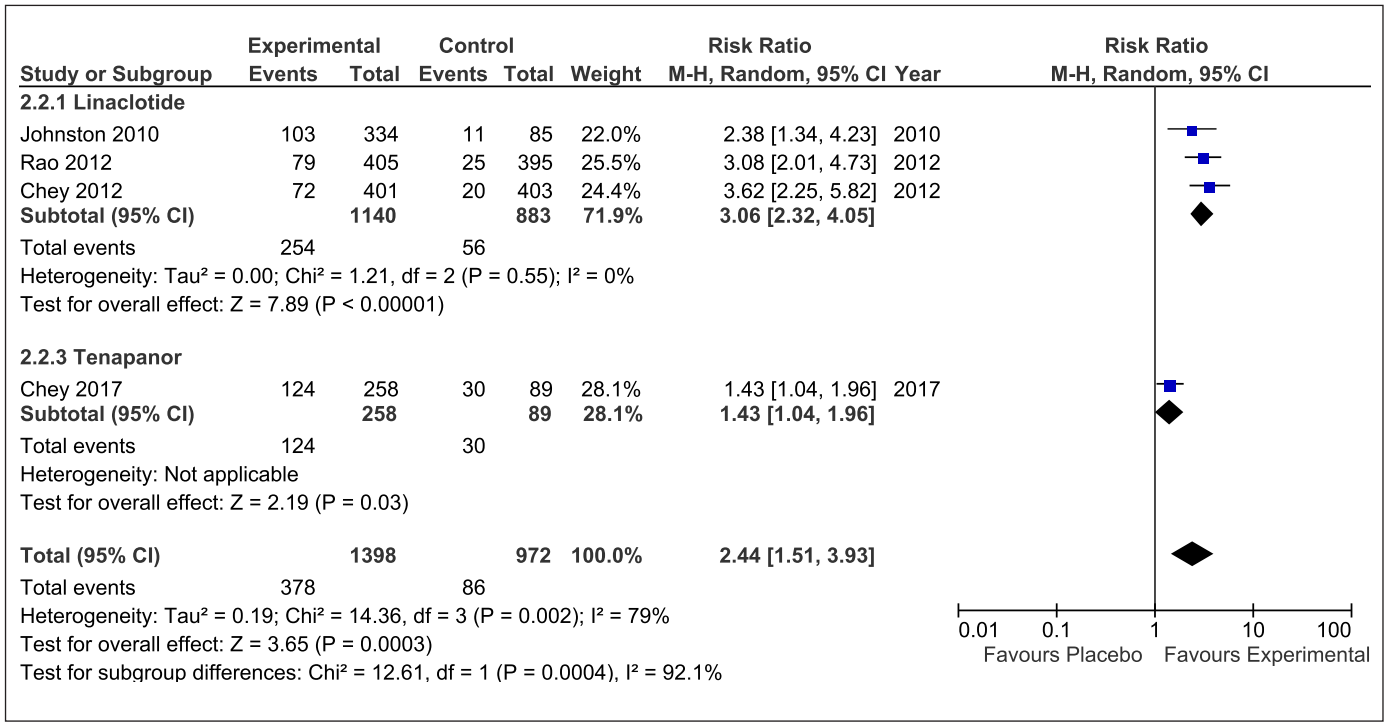

FIGURE 3. Efficacy of intestinal secretagogues on irritable bowel syndrome patients, based on the following endpoints: A) Increase in CSBM per week.

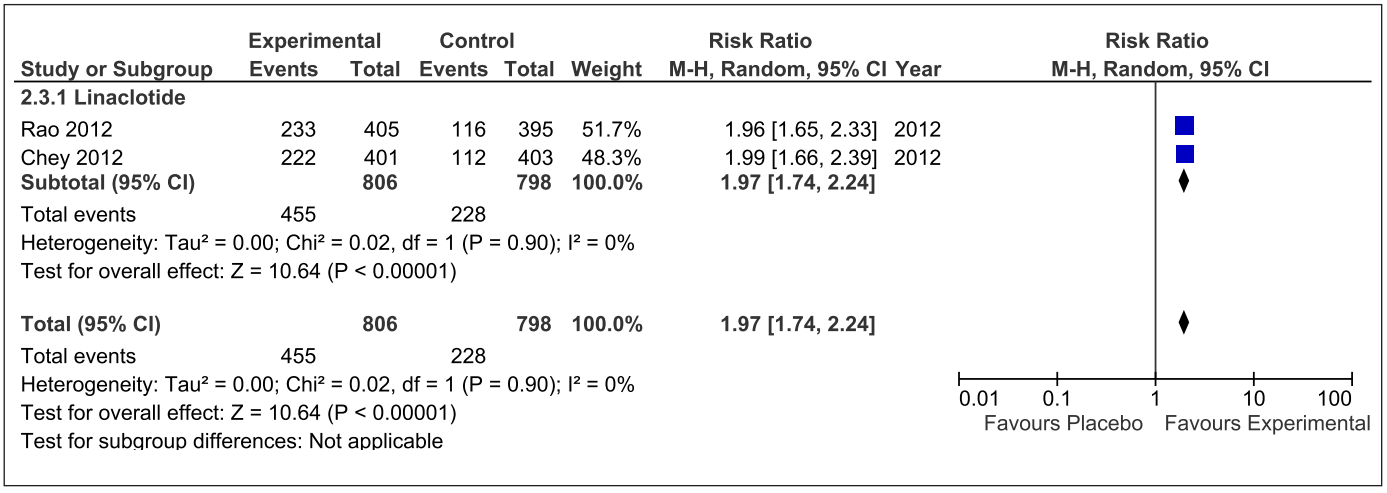

FIGURE 3. B) Achievement of >3 SBM per week.

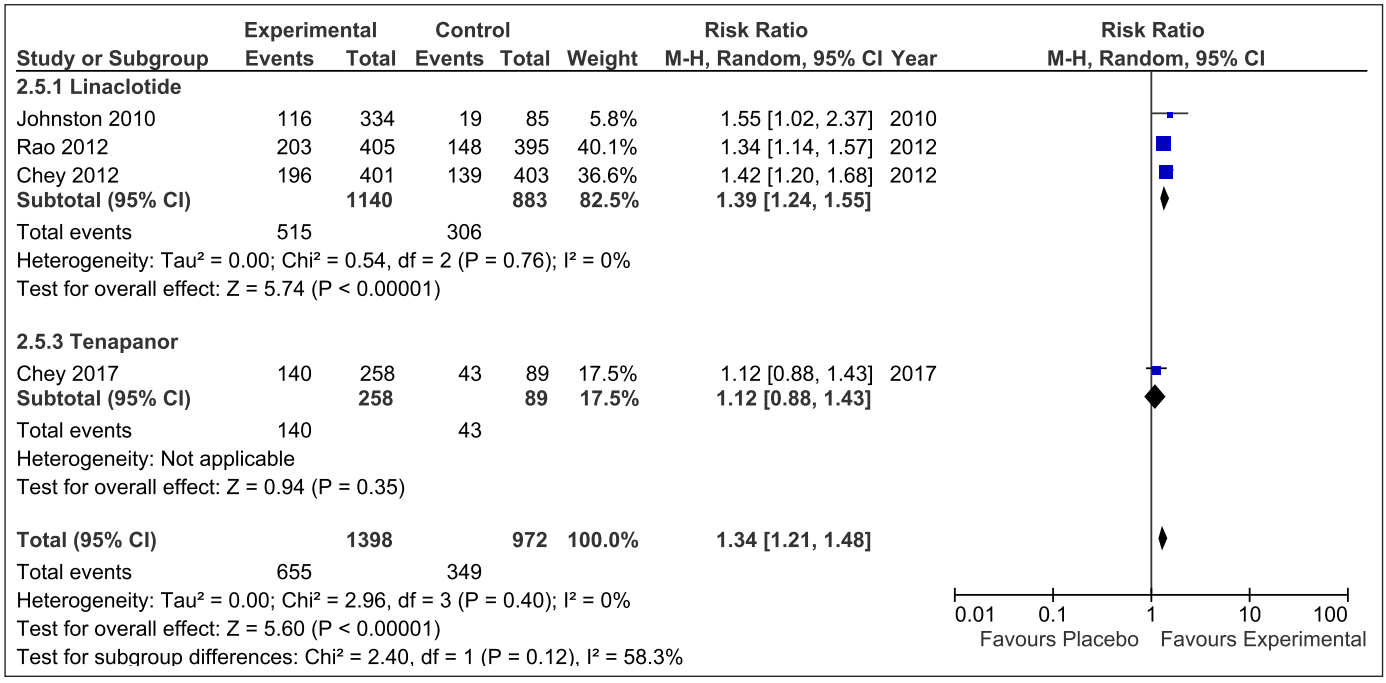

FIGURE 3. C) Improvement of abdominal pain; D) SBM after medication intake.

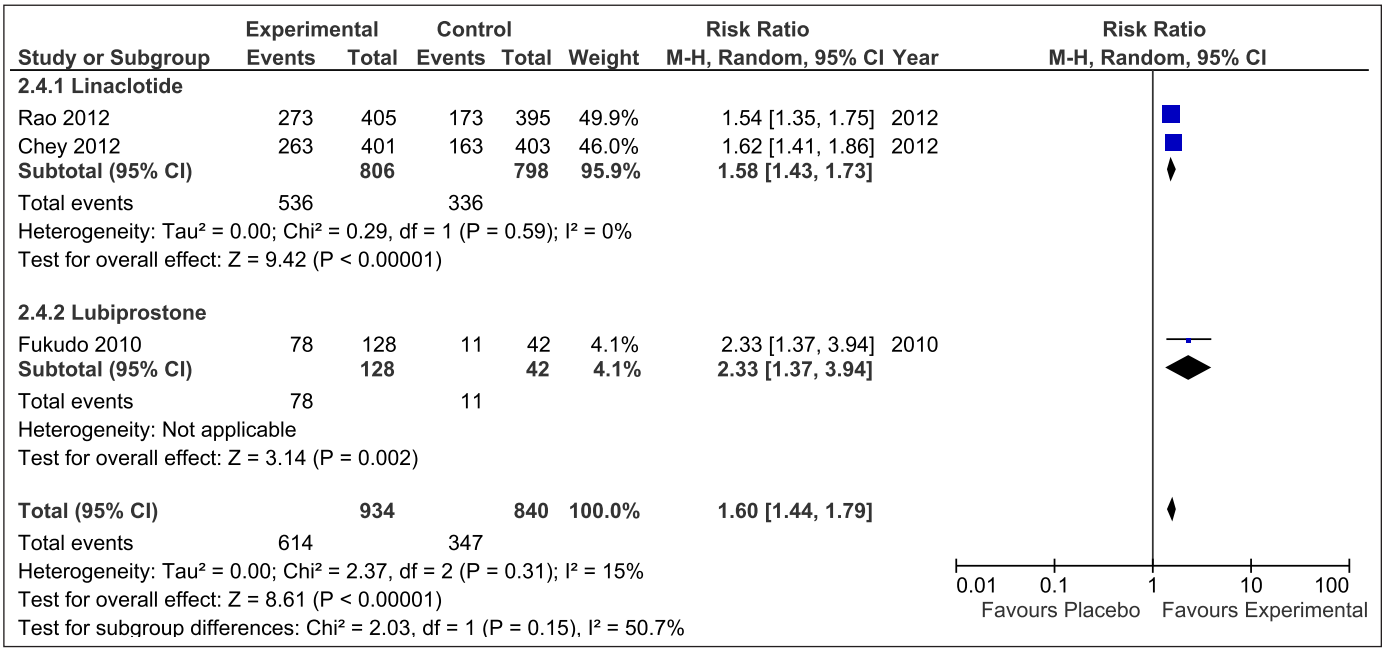

FIGURE 3. D) SBM after medication intake.

DISCUSSION

Constipation – in the context of CC or IBS-C – can be a very challenging condition to treat, leading to an impaired quality of life in a non-neglectable proportion of patients[2]. One of the reasons for this difficulty in the treatment is the paucity of therapeutic alternatives available. Most of the treatment options consist of laxatives as well as bulky agents such as fiber, which constitute a heterogeneous group of medications directed towards increasing the amount of water in stools or increasing colonic wall motility. A meta-analysis by Lee-Robichaud et al.[28] showed that, among the afore-mentioned options, polyethylene glycol was the laxative that showed more consistent results in terms of both efficacy and safety for the treatment of CC. Nevertheless, available alternatives other than laxatives are not abundant.

TABLE 3. Adverse events rates versus placebo.

AE	Number of studies	Number of patients on experimental drug	Number of patients on experimental drug and AE (%)	Number of patients on placebo	Number of patients on placebo and AE (%)	RR	CI 95%
LINACLOTIDE							
Diarrhea	6	2235	722	1377	47	9.46	7.1-12.61
Abdominal pain	6	2235	106	1377	45	1.45	1.03-2.04
Flatulence	5	1900	89	1292	41	1.47	1.02-2.18
LUBIPROSTONE							
Diarrhea	8	1691	131	1055	14	5.83	3.38-10.1
Nausea	7	1663	162	1029	42	2.38	1.71-3.32
Abdominal pain	6	779	51	626	19	2.15	1.28-3.61
PLECANATIDE							
Diarrhea	1	931	54	458	6	4.42	1.91-10.21
Nasopharyngitis	1	931	15	458	8	0.92	0.39-2.15
Sinusitis	1	931	13	458	3	2.13	0.61-7.44
TENAPANOR							
Diarrhea	1	266	28	90	0	N/A	N/A
Nausea	1	266	13	90	1	4.39	0.58-33.15
Abdominal pain	1	266	11	90	2	1.86	0.42-8.23

AE: adverse event.

Agents that promote adequate colonic motility such as 5-HT agonists have not been widely used until recently, mainly due to the concerns related to their potential cardiac side effects – as shown by the cisapride experience[7]. Prucalopride – a selective 5-HT4 agonist – has been approved by the European Medicines Agency for the treatment of CC due to its safety profile, showing no cardiac adverse events. Although prucalopride has expanded the therapeutic horizons for the treatment of CC or IBS-C, it may not be suitable or effective for every case that do not respond to laxatives or dietary measures.

Intestinal secretagogues are a type of medications whose mechanism of action implicates an increased amount of water excreted through the colonic epithelium. This is achieved by different means: linaclotide is a guanylate-cyclase agonist, whereas lubiprostone activates CIC-2 chloride channels, leading to the above-mentioned effect. Both plecanatide and tenapanor have been recently tested: plecanatide is also a guanylate-cyclase agonist like linaclotide[26]; tenapanor in change inhibits sodium intake by intestinal epithelial cells, by inhibiting the sodium-proton exchanger NHE3[27]. According to our result, regardless of the molecular approach these drugs have, intestinal secretagogues are more effective than placebo for the treatment of CC and IBS-C. This conclusion becomes relevant since evidently the mechanism exerted by these drugs is an effective one, thus it may provide significant information towards the design of new drugs with a similar mechanism. Moreover, these drugs seem to have acceptable safety profiles: there is a logical increase in the risk of gastrointestinal symptoms, which do not seem to represent a major threat to the patients under treatment.

Some interesting points should be mentioned when analyzing this systematic review. First of all, even though all of the clinical trials involved showed high quality from a methodological point of view, a non-neglectable heterogeneity in terms of outcome measurement was observed. With the exception of two trials[16,17] which adopted Food and Drug Administration's suggested endpoints, none of the included studies evaluated the outcomes in a uniform fashion – this is a relevant point when it comes to comparing the results of different trials and when meta-analyses are performed. An effort should be made for future trials to reach a consensus regarding endpoint consideration and measurement.

On the other hand, there is relevant information which has not been exhaustively assessed. As highlighted in TABLE 1, the vast majority of patients were allowed to receive rescue medications; and even though intestinal secretagogues showed a better performance in every single endpoint under consideration, the comparison of the amount of rescue medicine needed in both therapeutic arms becomes a valuable piece of information in a clinical scenario in which most endpoints are subjective – this information is not present in most of the clinical trials.

According to our results, it becomes clear that intestinal secretagogues are a useful tool for the treatment of CC and IBS-C. However, the exact place in the therapeutic algorithm of constipation-related syndromes is not clear. Placebo-controlled trials do not answer the question of whether these drugs are suitable to become first-line therapies. For this purpose, head to head comparisons between experimental drugs and standard of care treatments (such as polyethylene glycol for instance) are needed. There is a noticeable lack of evidence involving head to head comparisons: a network meta-analysis (with its obvious limitations) did not find any advantage among therapeutic alternatives for CC[29]. This network meta-analysis can arguably replace the need for non-inferiority clinical trials comparing different therapeutic approaches – prokinetics, laxatives, intestinal secretagogues.

In conclusion, intestinal secretagogues are both useful and safe for the treatment of both CC and IBS-C. A significant heterogeneity in terms of outcome measurement was observed, which can be detrimental for pooled analysis and therefore efforts should be made towards unifying endpoint selection criteria. Finally, head to head comparisons are necessary in order to establish a stepwise algorithm for the management of patients with CC and IBS-C.

Authors' contribution

Lasa JS: study design, bibliographic coordination, statistical analysis. Altamirano MJ: bibliographic search, data input. Bracho LF: bibliographic search, data input. Paz S: bibliographic search, data input. Zubiaurre I: study design, critical review of draft.

Lasa JS, Altamirano MJ, Bracho LF, Paz S, Zubiaurre I. Eficiência e segurança de secretagogos intestinais para constipação crônica: uma revisão sistemática e meta-análise. Arq Gastroenterol. 2018. Ahead of print.

RESUMO – **Contexto** – Os secretagogos intestinais têm sido testados para o tratamento da constipação crônica e síndrome do intestino irritável com constipação predominante. O efeito classe desses tipos de drogas ainda não foi estudado. **Objetivo** – Determinar a eficácia e a segurança de secretagogos intestinais para o tratamento da constipação crônica e síndrome do intestino irritável de constipação predominante. **Métodos** – Realizada pesquisa baseada em banco de dados de trabalhos publicados entre 1966 e setembro de 2017. A estratégia de pesquisa consistia dos seguintes termos MeSH: secretagogos intestinais OU linaclotide OU lubiprostona OU plecanatide OU tenapanor OU canal de cloro E constipação crônica OU síndrome do intestino irritável. Os dados foram extraídos como análises de intenção de tratar. Um modelo de efeitos aleatórios foi usado para dar uma estimativa mais conservadora do efeito das terapias individuais, permitindo a qualquer heterogeneidade entre os estudos. Os desfechos foram descritos como risco relativo de alcançar uma melhoria no sintoma em consideração. **Resultados** – A busca no banco de dados rendeu 520 citações bibliográficas: 16 ensaios foram incluídos para análise, que incluiu 7658 pacientes. Doze trabalhos avaliaram a eficácia de secretagogos intestinais para constipação crônica. Estes foram melhores do que placebo, alcançando um aumento no número de evacuações completas espontâneas por semana [RR 1,87 (1,24-2,83)], para a aquisição de três ou mais evacuações espontâneas por semana [RR 1,56 (1,31-1,85)] e na indução espontânea do movimento intestinal após a ingestão de medicação [RR 1,49 (1,07-2,06)]. Resultados semelhantes foram observados ao avaliar a eficácia de secretagogos intestinais na síndrome do intestino irritável de constipação predominante com base em resultados de seis ensaios. **Conclusão** – Os secretagogos intestinais são alternativas terapêuticas úteis e seguras para o tratamento de síndromes relacionadas à constipação.

DESCRITORES – Constipação intestinal. Síndrome do intestino irritável. Colo.

REFERENCES

1. Vakil N, Stelwagon M, Shea EP, Miller S. Symptom burden and consulting behavior in patients with overlapping functional disorders in the US population. United European Gastroenterol J 2016;4:431-22.
2. Enck P, Leinert J, Smid M, Kohler T, Schwille-Kiuntke J. Somatic comorbidity in chronic constipation: more data from the GECCO study. Gastroenterol Res Pract 2016;2016:5939238.
3. Drossman DA. Functional Gastrointestinal Disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology 2016;Feb 1. pii: S0016-5085(16)00223-7.
4. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016;1:133-46.
5. Jadallah KA, Kullab SM, Sanders DS. Constipation-predominant irritable bowel syndrome: a review of current and emerging drug therapies. World J Gastroenterol. 2014;20:8898-909.
6. Mearin F, Ciriza C, Minguez M, Rey E4, Mascort JJ5, Peña E, et al. Clinical practice guideline: irritable bowel syndrome with constipation and functional constipation in the adult. Rev Esp Enferm Dig. 2016;108:32-63.
7. Aboumarzouk OM, Agarwal T, Antakia R, Shariff U, Nelson RL. Cisapride for intestinal constipation. Cochrane Database Syst Rev. 2011;(1):CD007780.
8. Ryu HS, Choi SC. Recent updates on the treatment of constipation. Intest Res. 2015;13:297-305.
9. Love BL, Johnson A, Smith LS. Linaclotide: a novel agent for chronic constipation and irritable bowel syndrome. Am J Health Syst Pharm. 2014;71:1081-91.
10. Jin Y, Blikslager AT. ClC-2 regulation of intestinal barrier function: translation of basic science to therapeutic target. Tissue Barriers. 2015;3(4):e1105906.
11. Thomas RH, Luthin DR. Current and emerging treatments for irritable bowel syndrome with constipation and chronic idiopathic constipation: focus on prosecretory agents. Pharmacotherapy. 2015;35:613-30.
12. Schoenfeld P, Cook D, Hamilton F, Laine L, Morgan D, Peterson W. An evidence-based approach to gastroenterology therapy. Gastroenterology. 1998;114:1318-25.
13. Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139:1877-86.
14. Lembo AJ, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138:886-95.
15. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365:527-36.
16. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107:1702-12.
17. Rao SS, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107:1714-24.
18. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103:170-7.
19. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, Ueno R. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29:329-41.
20. Fukudo S, Hongo M, Kaneko H, Ueno R. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterol Motil. 2011;23:544-e205.
21. Ondo WG, Kenney C, Sullivan K, Davidson A, Hunter C, Jahan I, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;78:1650-4.
22. Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15:1825-34.
23. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13:294-301.

24. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol. 2015;110:725-32.
25. Christie J, Shroff S, Shahnavaz N, Carter LA, Harrison MS, Dietz-Lindo KA, et al. A randomized, double-blind, placebo-controlled trial to examine the effectiveness of lubiprostone on constipation symptoms and colon transit time in diabetic patients. Am J Gastroenterol. 2017;112:356-64.
26. Miner PB, Koltun WD, Wiener GJ, De La Portilla M, Prieto B, Shailubhai K, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol. 2017;112:613-21.
27. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol. 2017;112:763-74.
28. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev 2010;7:CD007570.
29. Nelson AD, Camilleri M, Chirapongsathorn S, Vijayvargiya P, Valentin N, Shin A, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. Gut. 2017;66:1611-22.