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Persistent constipation and abdominal adverse events with newer treatments for constipation

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ABSTRACT

Background: Clinical trials of several new treatments for opioid-induced constipation (OIC), chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C) have focused on differences between subjects relieved of constipation with placebo and active treatment. Patients and clinicians however, are more interested in the probability these treatments provide actual relief of constipation and its associated symptoms.

Methods: We searched the medical literature using MEDLINE and Cochrane central register of controlled trials. Randomised, placebo-controlled trials that examined the use of methylnaltrexone, naloxegol, lubiprostone, prucalopride or linaclotide in adults with OIC, CIC and IBS-C were eligible for inclusion. The primary efficacy measure was relief of constipation. Adverse event data for abdominal symptoms were also analysed.

Key results and findings: 25 publications were included in our analyses. The proportion of constipated individuals with active treatment was significantly lower than the proportion with placebo; however, in 15 of these 20 trials analysed, a majority of patients remained constipated with active treatment. Analyses of adverse event data revealed that the percentage of participants who experienced abdominal pain, diarrhoea and flatulence with active treatment was higher than that with placebo in the majority of trials analysed.

Conclusions: Newer pharmacological treatments for constipation are superior to placebo in relieving constipation, but many patients receiving active treatment may remain constipated. In addition, all 5 of the treatments studied are accompanied by no change or a possible increase in the prevalence of abdominal symptoms, such as abdominal pain, diarrhoea and flatulence.

Summary box

What is already known about this subject?

- Chronic constipation is a common problem that is difficult to treat.
- Patients often have continued symptoms despite conventional therapies.
- Newer pharmacological agents are available for patients with continued symptoms despite conventional therapies.

What are the new findings?

- In most clinical trials, a majority of patients treated with a newer agent remained constipated.
- These findings were seen across three types of constipation.
- These newer agents also do not change or actually increase the percentage of individuals with symptoms such as abdominal pain, diarrhoea and flatulence.

How might it impact on clinical practice in the foreseeable future?

- Clinicians should anticipate a high probability that with one of the newer treatments for constipation, a patient will remain constipated with persistent abdominal symptoms.

INTRODUCTION

Constipation affects up to 27% of the US population, and its incidence has been increasing.[1] Chronic constipation imposes a high burden of healthcare costs in that it results in over two million physician visits and nearly 100 000 hospitalisations per year.[2 3] Further, constipation-related emergency department visits have increased by 42% from 2006 to 2011, resulting in a 121% increase in associated costs.[4] Chronic constipation impairs the quality of life and can result in increased psychological stress and depression.[5 6] It is also often accompanied by other symptoms, such as abdominal pain and discomfort, stomach cramping, bloating and gas pain.[7]

There are different difficult defaecation types of constipation. Chronic idiopathic constipation (CIC) is defined as constipation in individuals with no apparent physiological abnormality.[8 9] Constipation-predominant irritable bowel syndrome (IBS-C) is defined by the presence of recurrent abdominal pain or discomfort at least 3 days/month over a 3-month period, which is accompanied by at least two of the following: improvement with

defaecation; onset associated with change of frequency of stool; or onset associated with change in form of stool.[9] Opioid-induced constipation (OIC) is defined as constipation in individuals taking opioid medications. Up to 81% of patients taking opioids experience constipation, which can result in a significant impact on their quality of life and activities of daily living,[10] and the incidence of OIC is expected to rise due to the increased number of narcotic prescriptions dispensed in the USA. Patients with OIC frequently have continued constipation despite the use of a laxative.[11 12]

Treatment of constipation initially involves fibre as well as over-the-counter osmotic and stimulant laxatives,[13] but many patients continue to have symptoms. For such patients, the American Gastroenterological Association recommends treatment with one of the newer pharmacological agents that have been approved by the US Food and Drug Administration (FDA), or the European Medicines Agency (EMA)—lubiprostone (FDA approval 1, 2006), methylnaltrexone (FDA approval 4, 2008), prucalopride (EMA approval 10, 2009), linaclotide (FDA approval 8, 2012) and naloxegol (FDA approval 9, 2014).[13 14] In clinical trials, each treatment has been statistically significantly superior to placebo in relieving constipation.[15–39] One problem, however, is that there is no clear, consistent relationship between the effect of a treatment on physiological processes in a constipated patient and its clinical effect on constipation.

The aim of our analyses was to examine the ability of these newer pharmacological agents to provide relief of constipation and its associated symptoms, including abdominal pain, diarrhoea, flatulence and bloating.

METHODS

We searched the medical literature using MEDLINE and the Cochrane central register of controlled trials, to identify publications that reported effects of these newer treatments on constipation. Search terms included the following as free-text terms: methylnaltrexone, naloxegol, lubiprostone, prucalopride or linaclotide. These terms were combined using the set operator AND with trials identified with the terms constipation, irritable bowel syndrome, opioid or trial. This search returned 1432 publications as of 1 March 2015. Some of these publications reported meta-analyses of effects of a particular treatment on constipation;[40–44] however, we did not include these publications in our analyses because they did not contain data that enabled us to determine the proportion of individuals who remained constipated with active treatment or placebo.

From the initial search, we selected all publications of trials in adult individuals that were placebo-controlled and that reported data for relief of constipation as well as adverse event data (N=25). From these 25 publications, we selected all publications that reported the number or percentage of participants with relief of constipation (N=20). Of the original 25 publications, 5 reported average number of bowel movements during a given period of time, or the change from number of baseline bowel movements instead of percentage, or number of individuals with relief of constipation.[21 24 26]

Data were extracted by two investigators (IS and JG) and placed onto a Microsoft Excel spreadsheet (Windows V.14.4.9, Microsoft, Redmond, Washington, USA). Each investigator created a separate database. The final 'locked database' was created after resolving all discrepancies between the two individual databases.

The primary efficacy measure was relief of constipation defined as (1) rescue-free laxation within 4 hours of first dose of study drug, (2) ≥3 complete spontaneous bowel movements (CSBMs) per week, and ≥1 CSBM per week from baseline for 75% of weeks, (3) ≥3–4 spontaneous bowel movements per week during week 4 of treatment or (4) average of ≥3 CSBMs per week over a 12-week period.

For each publication and for each treatment we calculated the percentage of patients who remained constipated at the end of the trial (ie, the percentage of individuals who failed to experience relief of constipation) as well as the percentage of participants who reported an abdominal symptom as an adverse event—abdominal pain, diarrhoea, flatulence or abdominal distension/bloating. In some instances, such as with abdominal pain and diarrhoea, the number of trials reporting values for one of these symptoms is greater than the number of trials included in our analyses of constipation because a trial may have reported adverse event data but did not report data that enabled us to calculate the percentages of individuals who remained constipated with active treatment and with placebo. In other instances, such as with flatulence or abdominal distension/bloating, the number of trials reporting values for one of these symptoms is less than the number of trials included in our analyses of constipation, because these symptoms were not reported in all trials included in our analyses of constipation. A database containing the extracted data used for all analyses in the present paper is provided in online supplementary table S1.

One-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test and Unpaired t-test with Welch correction were performed using GraphPad InStat V.3.10 for Windows; Sample size was calculated using GraphPad StatMate V.2.00 for Windows, GraphPad Software, La Jolla California, USA. Figures were prepared using Microsoft Excel for Windows V.14.4.9, Microsoft, Redmond, Washington, USA.

RESULTS

Twenty trials included sufficient information to calculate the number and percentage of participants who remained constipated at the end of the trial. Constipation was an entry criterion for each trial. Figure 1 displays the percentage of individuals who received active treatment or placebo and were

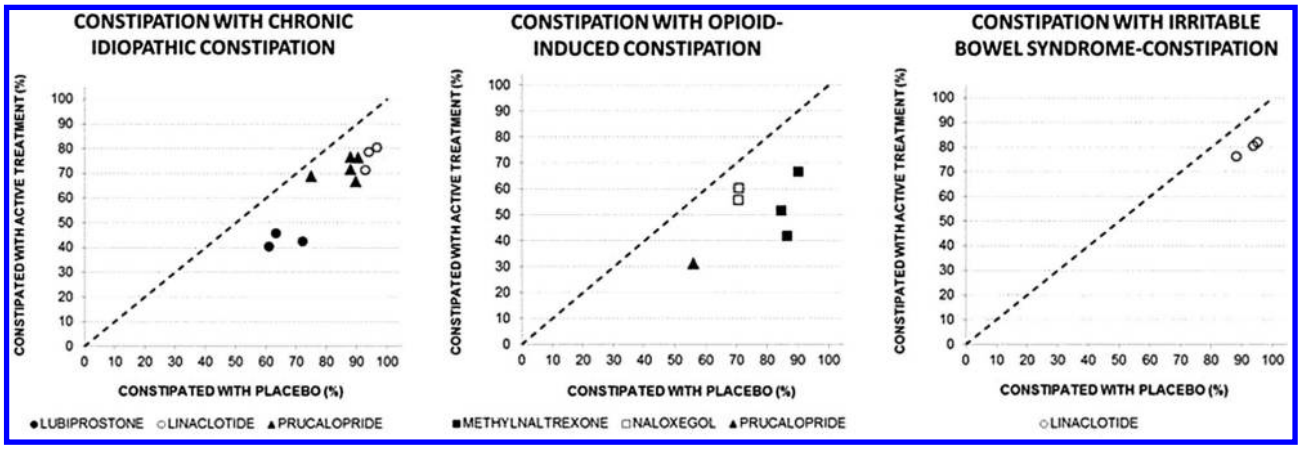

Figure 1 Relationship between constipation with active treatment and that with placebo. The percentage of individuals who were constipated with active treatment is plotted as a function of the corresponding value with placebo. If more than one dose of active treatment was tested in a particular trial, the value from the highest dose is analysed. The dashed diagonal line is the identity line. Symbols above the identity line indicate that the value for constipation with active treatment is higher than the corresponding value with placebo, and values below the identity line indicate the opposite.

constipated at the end of the trial stratified by type of constipation and then by active treatment. Results from each trial were below the identity line, indicating that the percentage of constipated patients with active treatment was less than the percentage of constipated individuals with placebo in the same trial. In all figures, the vertical and horizontal distances from any point to the identity line form the two equal sides of an isosceles triangle and represent the magnitude of the difference between active treatment and placebo.

Figure 1 (left) displays results from 11 trials in individuals with CIC. Results from the three trials of lubiprostone differed significantly from the five trials of prucalopride, and from the three trials of linaclotide (ANOVA $p<0.0001$ for active treatment and $p<0.0005$ for placebo). These results with placebo treatment indicate that with respect to the prevalence of constipation, participants in one group of trials are not exchangeable with participants in the other two groups of trials. In the lubiprostone trials, values for constipation with active treatment were significantly lower than corresponding values for active treatment in the prucalopride trials ($p<0.0001$ Tukey-Kramer Multiple Comparisons Test) and in the linaclotide trials ($p<0.0001$ Tukey-Kramer Multiple Comparisons Test). Also, in each of the eight trials of prucalopride and linaclotide, a majority of patients (67–81%) remained constipated with active treatment, whereas in the lubiprostone trials, only 40–46% of participants remained constipated with active treatment. Also, in the lubiprostone trials, values for constipation with placebo treatment were significantly lower than corresponding values for active treatment in the prucalopride trials ($p<0.001$ Tukey-Kramer Multiple Comparisons Test) and in the linaclotide trials ($p<0.0001$ Tukey-Kramer Multiple Comparisons Test). Moreover, these results raise the possibility that the increased effectiveness of lubiprostone compared with prucalopride and linaclotide in relieving idiopathic chronic constipation may have occurred simply because participants enrolled in the lubiprostone trials were less likely to remain constipated at the end of the trial regardless of whether they received placebo or active treatment. Evidence to support this possibility is that mean difference (95% CI) between the percentages of individuals constipated with active treatment and placebo in the lubiprostone trials (23 (6–39)) was not significantly different from the differences in the prucalopride (14 (6–22)) or linaclotide (18 (5–31)) trials.

Figure 1 (middle) displays results from six trials in patients with OIC. Values for constipation with active treatment in the three methylnaltrexone trials were not significantly different from values with active treatment in the two naloxegol trials ($p=0.602$; unpaired t-test with Welch correction). On the other hand, values for constipation with placebo treatment in the three methylnaltrexone trials were significantly higher than values with placebo treatment in the two naloxegol trials ($p=0.0099$; unpaired t-test with Welch correction). The single trial of prucalopride in OIC had a value for constipation with placebo treatment that was lower than values with placebo treatment in the methylnaltrexone and naloxegol trials making it likely that with respect to the prevalence of constipation, participants in trials with one of these three treatments are not exchangeable with individuals in trials with the other two treatments. In the two naloxegol trials, and two of the three methylnaltrexone trials, a majority of patients remained constipated with active treatment. In one of the methylnaltrexone trials, only 42% of participants remained constipated with active treatment; and in the single prucalopride trial, 31% of patients remained constipated with active treatment. Compared to the trials of methylnaltrexone and naloxegol, the increased effectiveness of the single trial of prucalopride in relieving OIC may have occurred

simply because participants enrolled in the prucalopride trial were less likely to remain constipated at the end of the trial regardless of whether they received placebo or active treatment.

Figure 1 (right) illustrates results from three trials of linaclotide in IBS-C. Although values for constipation with active treatment were lower than corresponding values with placebo (p=0.0012; paired t-test), the proportion of patients who remained constipated ranged from 88% to 95% with placebo, and from 76% to 82% with active treatment.

Considering all 20 trials with relief of constipation as an efficacy endpoint, as many as 44% of participants were no longer constipated after being treated with placebo. The percentage of individuals who remained constipated with active treatment varied from 31% to 82%, and in 15 of the 20 trials, a majority of participants remained constipated with active treatment.

Twenty-five trials gave the number or percentage of participants who reported abdominal pain as a spontaneous adverse event. Figure 2 displays the percentage of participants who reported abdominal pain with active treatment, or placebo stratified by type of constipation, and then by active treatment. Results from 22 of the 25 trials were above the identity line, indicating that the percentage of patients with abdominal pain with active treatment was greater than the percentage of individuals with abdominal pain with placebo in the same trial.

Figure 2 (left) displays results for abdominal pain from 13 trials in participants with CIC. Results from the five trials of prucalopride differed significantly from the five trials of lubiprostone, and from the three trials of linaclotide (ANOVA p=0.0049 for active treatment and p=0.0392 for placebo). These results with placebo treatment indicate that with respect to the prevalence of abdominal pain, individuals in one group of trials are not exchangeable with participants in the other two groups of trials. In the prucalopride trials, values for abdominal pain with active treatment were significantly higher than corresponding values for active treatment in the lubiprostone trials (p<0.05 Tukey-Kramer Multiple Comparisons Test) and in the linaclotide trials (p<0.05 Tukey-Kramer Multiple Comparisons Test). In the prucalopride trials, values for abdominal pain with placebo were significantly higher than corresponding values in the lubiprostone trials (p<0.05 Tukey-Kramer Multiple Comparisons Test) but not in the linaclotide trials (p>0.05 Tukey-Kramer Multiple Comparisons Test). Overall, the percentage of patients who experienced abdominal pain with placebo varied from 0% to 19%, and the percentage of individuals who experienced abdominal pain with active treatment varied from 0% to 38%. The percentages of patients with abdominal pain with active treatment were higher than the corresponding percentage with placebo in five of the five prucalopride trials, four of the five lubiprostone trials, but in only one of the three linaclotide trials.

Figure 2 (middle) displays results for abdominal pain from eight trials in participants with OIC. In the three methylnaltrexone trials, values for abdominal pain with active treatment or with placebo were not significantly different from corresponding values in the three naloxegol trials (active treatment p=0.725; placebo p=0.894; unpaired t-test with Welch correction). Values from the single prucalopride trial were in the same range as values from the trials of methylnaltrexone and naloxegol, whereas values from the single lubiprostone trial were lower than values from the other seven trials. Overall, the percentage of patients who experienced abdominal pain with placebo varied from 4% to 13%, and the percentage of individuals who experienced abdominal pain with active treatment varied from 4% to 38%. The percentages of participants with abdominal pain with active treatment were higher than the

Figure 2 Relationship between abdominal pain with active treatment and that with placebo. The percentage of individuals with abdominal pain with active treatment is plotted as a function of the corresponding value with placebo. If more than one dose of active treatment was tested in a particular trial, the value from the highest dose is analysed. The dashed diagonal line is the identity line. Symbols above the identity line indicate that the value for abdominal pain with active treatment is higher than the corresponding value with placebo, and values below the identity line indicate the opposite.

corresponding percentages with placebo in each of the eight trials of treatments for OIC.

Figure 2 (right) illustrates results for abdominal pain from three trials of linaclotide and one trial of lubiprostone in patients with IBS-C. Values for abdominal pain with active treatment were higher than corresponding values with placebo in each of the linaclotide trials but not in the lubiprostone trial.

Considering all 25 trials with abdominal pain reported as an adverse event, 0–19% of participants reported abdominal pain with placebo, and 0–38% of individuals reported abdominal pain with active treatment. Figure 2 also illustrates that with placebo, there were no significant differences among results from different types of constipation with respect to values for percentages of patients with abdominal pain (mean CIC 5.8%; OIC 6.5%; IBS-C 4.1%; ANOVA p=0.724). In contrast, with active treatment, values for percentages of subjects with abdominal pain and OIC (mean 20.3%) were significantly higher (ANOVA p=0.0019) than those for CIC (mean 8.2%; p<0.01 Tukey-Kramer Multiple Comparisons Test), and those for IBS-C (5.5%; p<0.01 Tukey-Kramer Multiple Comparisons Test). Results with active treatment for abdominal pain with CIC were not significantly different from those for IBS-C (p>0.05 Tukey-Kramer Multiple Comparisons Test).

Twenty-five trials gave the number or percentage of patients who reported diarrhoea as a spontaneous adverse event. Figure 3 displays the percentage of patients who reported diarrhoea with active treatment, or placebo stratified by type of constipation and then by active treatment. Results from 24 of the 25 trials were above the identity line, indicating that the percentage of individuals with diarrhoea with active treatment was greater than the percentage of patients with diarrhoea with placebo in the same trial.

Figure 3 (left) displays results for diarrhoea from 13 trials in participants with CIC. There were no significant differences among the five trials of prucalopride, the five trials of lubiprostone and the three trials of linaclotide for the percentages of patients with diarrhoea with active treatment or placebo (ANOVA p=0.683 for active treatment and p=0.054 for placebo). Overall, the percentage of individuals who experienced diarrhoea with placebo varied from 0% to 8%, and the percentage of participants who experienced diarrhoea with active treatment varied from 3% to 22%. The percentages of patients with diarrhoea with active treatment were higher than the corresponding percentage with placebo in all trials of prucalopride, lubiprostone and linaclotide.

Figure 3 (middle) displays results for diarrhoea from seven trials in participants with OIC. In the two methylnaltrexone trials, values for diarrhoea with active treatment or with placebo were not significantly different from corresponding values in the three naloxegol trials (active treatment p=0.075; placebo p=0.293; unpaired t-test with Welch correction). Values from the single prucalopride trial, and from the single lubiprostone trial were in the same range as values from the trials of methylnaltrexone and naloxegol. Overall, the percentage of participants who experienced diarrhoea with placebo varied from 2% to 6%, and the percentage of individuals who experienced diarrhoea with active treatment varied from 6% to 13%. The percentages of patients with diarrhoea with active treatment were higher than the corresponding percentages with placebo in each of the seven trials of treatments for OIC.

Figure 3 (right) illustrates results for diarrhoea from three trials of linaclotide and two trials of lubiprostone in IBS-C. In the two lubiprostone trials, values for

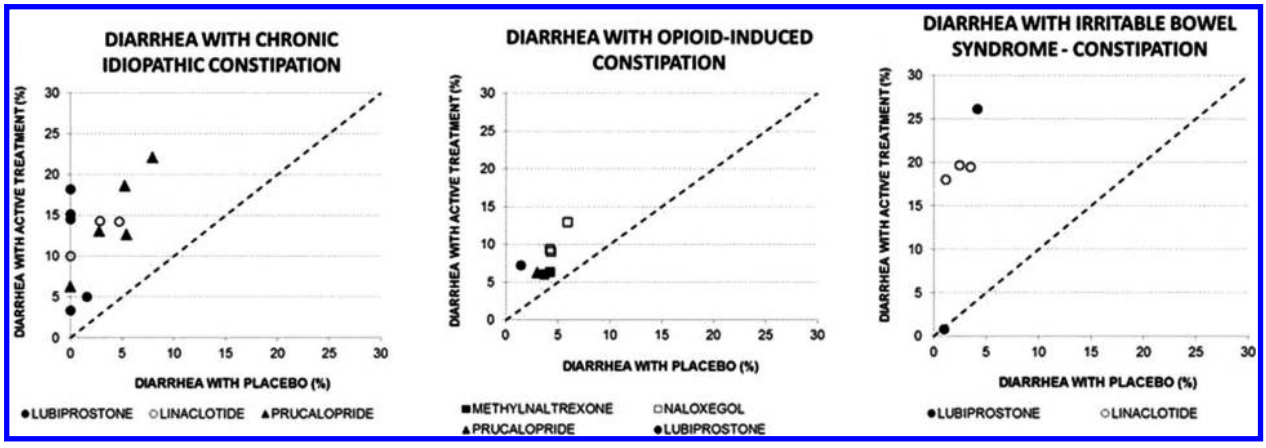

Figure 3 Relationship between diarrhoea with active treatment and that with placebo. The percentage of participants with diarrhoea with active treatment is plotted as a function of the corresponding value with placebo. If more than one dose of active treatment was tested in a particular trial, the value from the highest dose is analysed. The dashed diagonal line is the identity line. Symbols above the identity line indicate that the value for diarrhoea with active treatment is higher than the corresponding value with placebo, and values below the identity line indicate the opposite.

diarrhoea with active treatment or with placebo were not significantly different from corresponding values in the three linaclotide trials (active treatment p=0.734; placebo p=0.926; unpaired t-test with Welch correction). Overall, the percentage of individuals with IBS-C who experienced diarrhoea with placebo varied from 1% to 4%, and the percentage of patients who experienced diarrhoea with active treatment varied from 1% to 26%. The percentages of participants with diarrhoea with active treatment were higher than the corresponding percentages with placebo in each of the three linaclotide trials and one of the two lubiprostone trials.

Considering all 25 trials with diarrhoea as adverse events, 0–8% of participants reported diarrhoea with placebo, and 1–26% of individuals reported diarrhoea with active treatment. Figure 3 also illustrates that with placebo, there were no significant differences among results from different types of constipation with respect to values for percentages of patients with diarrhoea (mean CIC 3.8%; OIC 2.4%; IBS-C 2.5%; ANOVA p=0.356). Similarly, with active treatment, there were no significant differences among results from different types of constipation with respect to values for percentages of individuals with diarrhoea (mean CIC 12.9%; OIC 8.2%; IBS-C 16.8%; ANOVA p=0.056). On the other hand, the p value of 0.056 raises the possibility that with more trials, there might be significant differences among the active treatments with respect to values for percentages of patients with diarrhoea.

Seventeen trials gave the number or percentage of individuals who reported flatulence as a spontaneous adverse event. Figure 4 displays the percentage of participants who reported flatulence with active treatment or placebo stratified by type of constipation and then by active treatment. Percentage of patients with flatulence with active treatment was greater than the percentage of individuals with flatulence with placebo in the same trial.

Figure 4 (left) displays results for flatulence from eight trials in patients with CIC. There were no significant differences among two trials of prucalopride, the three trials of lubiprostone and the three trials of linaclotide for the percentages of individuals with flatulence with active treatment or placebo (ANOVA p=0.187 for active treatment, and p=0.185 for placebo). Overall, the percentage of patients who experienced flatulence with placebo varied from 0% to 9%, and the percentage of participants who experienced flatulence with active treatment varied from 0% to 8%. The percentages of patients with flatulence with active treatment were higher than the corresponding percentage with placebo in one of two trials of prucalopride, two of three trials of lubiprostone, and none of the three trials of linaclotide.

Figure 4 (middle) displays results for flatulence from six trials in patients with OIC. In the two methylnaltrexone trials, values for flatulence with active treatment or with placebo were not significantly different from corresponding values in the three naloxegol trials (active treatment p=0.083; placebo p=0.294; unpaired t-test with Welch correction). The value for flatulence with placebo from the single lubiprostone trial was in the same range as values with placebo from the trials of methylnaltrexone and naloxegol, but the value for flatulence with lubiprostone was lower than values with methylnaltrexone and naloxegol. Overall, the percentage of individuals who experienced flatulence with placebo varied from 1% to 7%, and the percentage of participants who experienced flatulence with active treatment varied from 4% to 14%. The percentages of patients with flatulence with active treatment were higher than the corresponding percentages with placebo in each of the six trials of treatments for OIC.

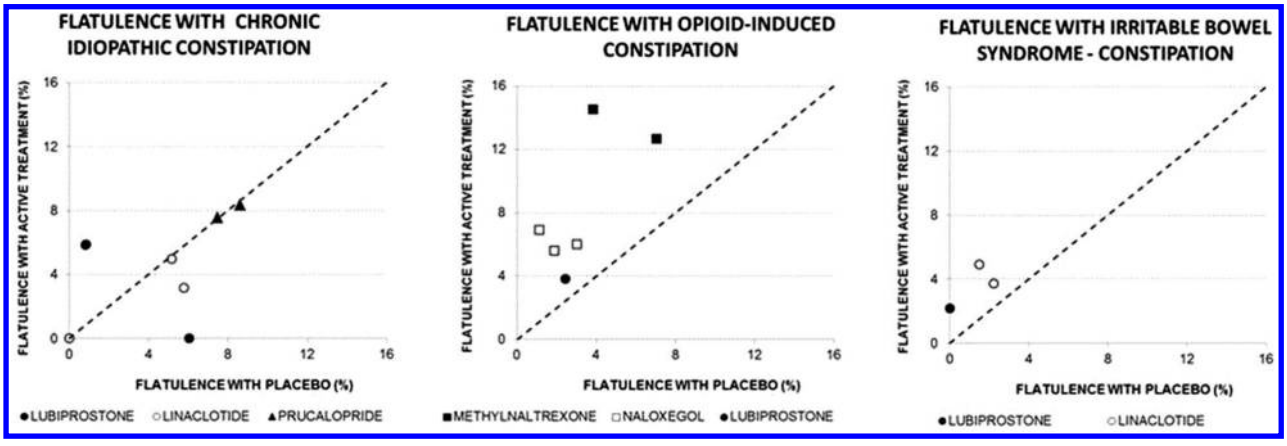

Figure 4 Relationship between flatulence with active treatment and that with placebo. The percentage of patients with diarrhoea with active treatment is plotted as a function of the corresponding value with placebo. If more than one dose of active treatment was tested in a particular trial, the value from the highest dose is analysed. The dashed diagonal line is the identity line. Symbols above the identity line indicate that the value for flatulence with active treatment is higher than the corresponding value with placebo, and values below the identity line indicate the opposite.

Figure 4 (right) illustrates results for flatulence from two trials of linaclotide and one trial of lubiprostone in IBS-C. Overall, the percentage of participants with IBS-C who experienced flatulence with placebo varied from 0% to 2%, and the percentage of individuals who experienced flatulence with active treatment varied from 2% to 5%. The percentages of patients with flatulence with active treatment were higher than the corresponding percentages with placebo in each of the three trials of treatments for IBS-C.

Considering all 17 trials with flatulence as adverse events, 0–9% of participants reported flatulence with placebo and 0–14% of patients reported flatulence with active treatment. Figure 4 also illustrates that with placebo, there were no significant differences among results from different types of constipation with respect to values for percentages of individuals with flatulence (mean CIC 4.4%; OIC 3.2%; IBS-C 1.2%; ANOVA p=0.262). Similarly, with active treatment, there were no significant differences among results from different types of constipation with respect to values for percentages of patients with flatulence (mean CIC 4.5%; OIC 8.2%; IBS-C 3.6%; ANOVA p=0.102).

Ten trials gave the number or percentage of participants who reported bloating or abdominal distension as a spontaneous adverse event. Figure 5 displays the percentage of individuals who reported bloating or abdominal distension with active treatment or placebo stratified by type of constipation and then by active treatment. Results from five of the 10 trials were above the identity line, indicating that the percentage of patients with bloating or abdominal distension with active treatment was greater than the percentage of participants with bloating or abdominal distension with placebo in the same trial.

Considering all 10 trials with bloating or abdominal distension as spontaneous adverse events, the percentage of patients who experienced flatulence with placebo varied from 1% to 10%, and the percentage of participants who experienced flatulence with active treatment varied from 0% to 11%. Furthermore, of these 10 trials, seven compared lubiprostone with placebo. In the three trials of CIC that tested lubiprostone (figure 5 (left)), values for bloating or abdominal distension with lubiprostone were lower than corresponding values with placebo. In the single trial of OIC that tested lubiprostone (figure 5 (middle)), the value for bloating or abdominal distension with lubiprostone was higher than the corresponding value with placebo. In the two trials of IBS-C that tested lubiprostone (figure 5 (right)), values for bloating or abdominal distension with lubiprostone were lower than corresponding values with placebo in one of the two trials. In the two trials of IBS-C that tested linaclotide (figure 5 (right)), values for bloating or abdominal distension with linaclotide were higher than corresponding values with placebo in both trials.

DISCUSSION

In the trials of treatment for constipation, all participants had to be constipated at study entry. We were surprised to find, however, that although the percentage of patients who remained constipated at the end of the trial with active treatment was lower than that with placebo in all 20 trials, in 15 of 20 (75%) trials, a majority of subjects who received active treatment remained constipated at the end of the trial. This phenomenon occurred with treatment for CIC, OIC and IBS-C. In those trials where only a minority of remained constipated with active treatment, a minority of participants also tended to remain constipated with placebo. Thus, this apparent increased effectiveness of active treatment may have occurred simply because participants enrolled in the trials were less likely to remain constipated at the end of the trial, regardless of whether they received placebo or active treatment.

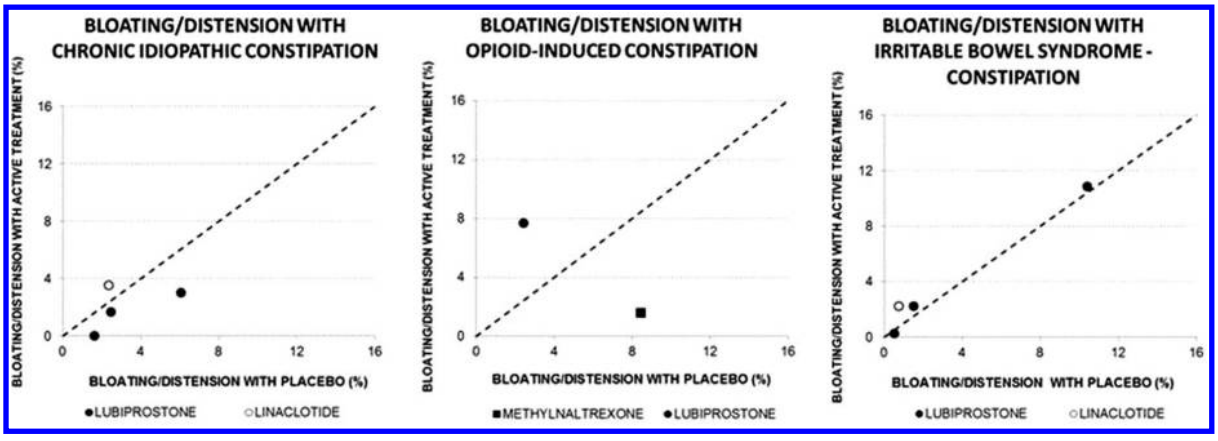

Figure 5 Relationship between bloating or distension with active treatment and that with placebo. The percentage of patients with diarrhoea with active treatment is plotted as a function of the corresponding value with placebo. If more than one dose of active treatment was tested in a particular trial, the value from the highest dose is analysed. The dashed diagonal line is the identity line. Symbols above the identity line indicate that the value for bloating or distension with active treatment is higher than the corresponding value with placebo, and values below the identity line indicate the opposite.

Furthermore, across all trials, the percentage of individuals with an abdominal adverse effect was generally higher with active treatment than with the corresponding placebo. Thus, in a majority of trials, not only did most subjects remain constipated with active treatment, and also the prevalence of abdominal symptoms, such as abdominal pain, diarrhoea, and flatulence increased with active treatment compared with placebo. These side effects may have a profound impact on the patient, especially in pain-predominant syndromes like IBS-C, where treatment is not only focused on constipation relief and also in relieving pain, oftentimes with antidepressants and psychological interventions.

In the 20 trials of treatments for constipation, the percentage of individuals who received placebo and remained constipated at the end of the trial ranged from 56% to 97%. In trials of CIC as well as of OIC, the percentage of patients who remained constipated in the placebo arms of the various active treatments differed significantly from each other. These findings indicate, for example, that in trials of CIC, subjects who received lubiprostone, prucalopride or linaclotide were not exchangeable with subjects in the other two groups. This variation makes it difficult for clinicians to decide on a particular treatment for constipation. This variation can also pose problems for investigators who design trials for treatments of constipation in that the number of subjects who will be required to detect a treatment effect of a particular magnitude will depend on the percentage of participants who are constipated with placebo treatment. For example, if 90% of patients who receive placebo will remain constipated at the end of the trial, a sample size of 60 patients per treatment group will have 90% power to detect a decrease of 24% with active treatment with a two-sided α of 0.05.[45] On the other hand, if 60% of subjects who receive placebo will remain constipated at the end of the trial, a sample size of 90 subjects per treatment group will be required to have 90% power to detect a decrease of 24% with active treatment with a two-sided α of 0.05.

The percentages of individuals with OIC who received active treatment and experienced abdominal pain were significantly higher than the percentages with CIC or IBS-C who received active treatment and experienced abdominal pain. This difference cannot be accounted for by the opioid receptor antagonist exerting a central effect and unblocking the analgesic effect of opioids, because possible changes in opioid-induced analgesia were examined in the clinical trials and none were found.[15–19] An alternative possibility is that opioid-induced decreased bowel motility, which is believed to account for the constipation, is reversed by active treatment and the resulting increased bowel activity may produce abdominal pain.

A number of publications that we analysed mentioned the use of rescue medication, which refers to the unblinded use of treatment for constipation in addition to the blinded treatments under investigation. Although we believe that all trials probably employed rescue medication, some publications provided detailed descriptions of the conditions under which rescue medication was to be used, such as three consecutive days without a bowel movement,[15 18–21 26 28–31 33 37 39] whereas, other publications only mentioned use of rescue medication in passing[34 38] or not at all. Except for the reports of trials with methylnaltrexone, which used an efficacy endpoint of laxation within 4 hours of administration of treatment, no publication provided a clear description of how administration of rescue medication influenced analysis of the trial results. Except for the trials of methylnaltrexone, all other trials defined constipation as fewer than three bowel movements during a 7-day period, and it seems to us that the use of rescue medication may have inflated the proportion of patients who experienced constipation in a given trial that did not involve methylnaltrexone.

Each trial included in our analyses assessed adverse events using the standard open-ended or free-response format. This has the advantage of not depending on asking individuals about symptoms that have been prespecified by the investigator or by a standard questionnaire, and therefore, may generate findings that might otherwise have been overlooked—a particularly important issue for pharmaceutical products. Also, an open-ended response is likely to reduce the 'noise' from positive responses from placebo participants, and thereby make it easier to detect adverse events associated with active treatments. A limitation of open-ended questions, however, is that it is not known whether a patient's failure to report a symptom occurred because there was no symptom or simply because it was not asked for.

Analyses of symptom data from the same trials using open-ended responses recorded in the adverse data compared to responses to prespecified questions regarding the same symptoms illustrate how these two approaches to symptom assessment can result in markedly different results. In our analyses, we included results from two trials of the effect of linaclotide in patients with CIC reported by Lembo *et al*.[34] Combined results from these two trials indicated that with placebo, linaclotide 145 µg and linaclotide 290 µg, the percentages of individuals with abdominal pain as an adverse event were 4.7%, 7.0% and 5.9%, respectively; and the percentages of participants with abdominal bloating as an adverse event were 2.4%, 3.5% and 3.6%, respectively. Chang *et al*[46] analysed data from daily responses prespecified questions regarding abdominal symptoms in the same two trials, and reported that the percentages of participants who experienced abdominal pain, abdominal discomfort or abdominal bloating on at least 1 day during a 2-week baseline period were 91%, 96% and 97%, respectively. We believe that the results from the analyses by Chang *et al* may represent a situation where a prespecified question increases the 'noise' in the data and obscures differences between placebo and active treatment.

One limitation to our analyses is that grouping publications by the different clinical types of constipation, and then subdividing each group on the basis of the active treatment tested, we often ended up with a small number of trials for a given active treatment that may have prevented us from identifying differences among various treatments or their accompanying placebos. For example, for participants who reported abdominal bloating or distension, there were four trials of patients with CIC (three with lubiprostone and one with linaclotide), two trials of patients with OIC (one with lubiprostone and one with methylnaltrexone) and four trials of IBS-C (three with lubiprostone and one with linaclotide).

There was no consistent relationship among the percentages of individuals who experienced a particular abdominal symptom with active treatment. For example, there were significant differences among participants treated with lubiprostone, prucalopride or linaclotide with respect to the percentages of individuals with abdominal pain, but not with respect to the percentages of patients with diarrhoea or flatulence. We have also been unable to identify any particular pharmacological mechanism of action that might account for our finding increased abdominal symptoms with active treatment. Both linaclotide and lubiprostone stimulate intestinal secretion of fluid and electrolytes,[47 48] and this action might account for diarrhoea; however, the values for the percentage of individuals who experienced diarrhoea with these agents were in the same range as those with prucalopride, which has a different mechanism of action.[49] Further, there are few studies investigating the effect these medications have on gastrointestinal transit, and whether increasing transit has a direct effect on symptom improvement or the development of side effects.

In summary, although the newer pharmacological treatments for constipation are superior to placebo in relieving constipation, many patients receiving active treatment are left constipated. Further, all five of these new treatments are associated by either no change or possibly an increase in abdominal pain, diarrhoea and flatulence.

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Supplemental Table 1: Numbers of subjects with relief of constipation or that experienced an abdominal symptom

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
N Engl J Med 2008; 358:2332-43.	OIC	Methylnaltrexone	PBO	Laxation within 4 hrs of 1st dose	71	11	71	9	3	5	6
		Methylnaltrexone	0.15mg/kg		62	30	63	11	4	8	1
Journal Supportive Oncology 2009; 7:39-46	OIC	Methylnaltrexone	PBO	Laxation within 4 hrs of 1st dose	52	7	52	2	X	2	X
		Methylnaltrexone	0.15mg/kg		47	29	47	13	X	6	X
		Methylnaltrexone	0.30mg/kg		55	32	55	21	X	8	X
Journal of Pain 2011; 12:554-562	OIC	Methylnaltrexone	PBO	Laxation within 4 hrs of 1st dose	162	16	162	6	6	X	X
		Methylnaltrexone	12mg QD		150	50	150	29	9	X	X
		Methylnaltrexone	12mg QOD		148	52	148	23	17	X	X
N Engl J Med 2014; 370:2387-96.	OIC	Naloxegol-04	PBO	$\geq$ 3 CSBMs per week + Increase $\geq$ 1 CSBMs per week from baseline for 9 of 12 of weeks & at least 3 of 4 final weeks	214	63	213	11	9	4	X
		Naloxegol-04	12.5mg		213	87	211	21	7	9	X
		Naloxegol-04	25mg		214	95	214	38	20	12	X
		Naloxegol-05	PBO		232	68	231	21	10	7	X
		Naloxegol-05	12.5mg		232	81	230	30	18	4	X
		Naloxegol-05	25mg		232	92	232	50	21	14	X
Aliment Pharmacol & Ther 2014; 40:771-779	OIC	Naloxegol	Usual Care	NONE	X	X	270	12	16	3	X
		Naloxegol	25mg		X	X	534	122	69	37	X

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
Am J Gastroenterol 2008; 103:170–177.	CIC	Lubiprostone	PBO	≥ 3 SBMs per week during week 4	122	34	122	1	2	1	3
		Lubiprostone	24ug bid		120	69	120	6	6	7	2
Aliment Pharmacol & Ther 2007; 25:1351-1361	CIC	Lubiprostone	PBO	Average # SBMs per week	X	X	33	1	0	2	2
		Lubiprostone	24ug/day		X	X	29	0	3	0	0
		Lubiprostone	48ug/day		X	X	32	1	2	0	3
		Lubiprostone	72ug/day		X	X	33	3	5	0	1
Pain Medicine 2014; 15:1825-1834	OIC	Lubiprostone	PBO	Change from baseline in # SBMs per week	X	X	206	8	3	5	5
		Lubiprostone	24ug bid		X	X	208	9	15	8	16
Dig Dis & Sciences 2010; 55:1090-1097	CIC	Lubiprostone	PBO	≥ 4SBMs per week during week 4	118	46	118	5	0	1	X
		Lubiprostone	24ug bid		119	71	119	8	4	7	X
Neurogastroenterol Motil 2011; 23:544-552	CIC +/- IBS-C	Lubiprostone	PBO	Change from baseline in # SBMs per week	X	X	42	1	0	X	X
		Lubiprostone	8ug bid		X	X	41	0	0	X	X
		Lubiprostone	16ug bid		X	X	43	1	4	X	X
		Lubiprostone	24ug bid		X	X	44	0	8	X	X
Clin Gastro & Hepatol 2015; 13:294-301	CIC	Lubiprostone-Study 1	PBO	≥ 4SBMs per week during week 4	60	22	62	1	0	X	1
		Lubiprostone-Study 1	24ug bid		59	32	62	2	9	X	0
		Lubiprostone-Study 2	PBO	Open label; no placebo - 48 weeks	X	X	X	X	X	X	6
		Lubiprostone-Study 2	24ug bid		X	X	209	11	78	X	7

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
Aliment Pharmacol & Ther 2008; 27:685-696	IBS-C	Lubiprostone	PBO	Change from baseline in # SBMs per week	X	X	48	3	2	0	5
		Lubiprostone	8ug bid		X	X	52	4	7	1	1
		Lubiprostone	16ug bid		X	X	49	3	6	2	5
		Lubiprostone	24ug bid		X	X	46	2	12	1	5
Aliment Pharmacol & Ther 2009; 29:329-341	IBS-C	Lubiprostone	PBO	# SBMs per week	X	X	387	X	4	X	2
		Lubiprostone	8ug bid		X	X	779	X	6	X	2
N Engl J Med 2008; 358:2344-54.	CIC	Prucalopride	PBO	Average of $\geq$ 3 CSBMs per week for 12 of weeks	209	25	209	40	11	18	X
		Prucalopride	2mg		207	64	207	46	28	23	X
		Prucalopride	4mg		204	58	204	40	38	17	X
Aliment Pharmacol & Ther 2009; 29:315-328	CIC	Prucalopride	PBO	Average $\geq$ 3 CSBMs per week over 12 week period	207	25	212	21	6	X	X
		Prucalopride	2mg		209	50	214	39	26	X	X
		Prucalopride	4mg		204	48	215	37	28	X	X
Gut 2009; 58:357-365	CIC	Prucalopride	PBO	Average $\geq$ 3 CSBMs per week over 12 week period	240	23	240	41	13	18	X
		Prucalopride	2mg		236	46	238	55	31	21	X
		Prucalopride	4mg		237	56	238	44	30	18	X
Neurogastroenterol Motil 2010; 22:991-999	CIC	Prucalopride	PBO	$\geq$ 3 CSBMs during week 4	72	18	72	4	0	X	X
		Prucalopride	1mg		76	33	76	7	5	X	X
		Prucalopride	2mg		75	28	75	3	1	X	X
		Prucalopride	4mg		80	25	80	9	5	X	X

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
Neurogastroenterol Motil 2012; 24:999-1009	CIC	Prucalopride	PBO	Average ≥ 3 CSBMs per week over 12 week period	252	26	252	6	20	X	X
		Prucalopride	2mg		249	83	249	17	55	X	X
Dig Dis & Sciences 2010; 55:2912-2921	OIC	Prucalopride	PBO	≥ 3 CSBMs per week over 4 week period	66	29	66	6	2	X	X
		Prucalopride	2mg		66	40	66	8	0	X	X
		Prucalopride	4mg		64	44	64	16	4	X	X
N Engl J Med 2011; 365:527-536.	CIC	Linaclotide Trial 303	PBO	≥ 3 CSBMs per week + Increase ≥ 1 CSBMs per week from baseline for 9 of 12 of weeks	209	7	424	20	20	22	10
		Linaclotide Trial 303	145ug		217	46	430	30	69	24	15
		Linaclotide Trial 303	290ug		216	42	422	25	60	21	15
		Linaclotide Trial 01	PBO		215	13	X	X	X	X	X
		Linaclotide Trial 01	145ug		213	34	X	X	X	X	X
		Linaclotide Trial 01	290ug		202	43	X	X	X	X	X
Am J Gastroenterol 2009 104:125-132	CIC	Linaclotide	PBO	#CSBMs per week	X	X	10	0	0	0	X
		Linaclotide	100ug		X	X	12	0	2	0	X
		Linaclotide	300ug		X	X	10	2	1	1	X
		Linaclotide	1000ug		X	X	10	0	1	0	X

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
Gastroenterology 2010;138:886-895	CIC	Linaclotide	PBO	≥ 3 CSBMs per week + Increase ≥ 1 CSBMs per week from baseline 3 of 4 of weeks	69	5	69	3	2	4	X
		Linaclotide	75ug		59	11	59	2	3	2	X
		Linaclotide	150ug		56	15	56	5	5	3	X
		Linaclotide	300ug		62	19	62	2	3	2	X
		Linaclotide	600ug		63	18	63	2	9	2	X
Gastroenterology 2010;139:1877-1886	IBS-C	Linaclotide	PBO	≥ 3 CSBMs per week + Increase ≥ 1 CSBMs per week from baseline 75% of weeks	85	10	85	3	1	X	X
		Linaclotide	75ug		79	20	79	4	9	X	X
		Linaclotide	150ug		82	16	82	3	10	X	X
		Linaclotide	300ug		84	27	85	4	14	X	X
		Linaclotide	600ug		89	21	89	7	16	X	X
Am J Gastroenterol 2012; 107:1702-1712	IBS-C	Linaclotide	PBO	≥ 3 CSBMs per week + Increase ≥ 1 CSBMs per week from baseline 9 of 12 weeks	403	20	403	16	10	9	6
		Linaclotide	290ug		401	72	402	18	79	15	9

PUBLICATION	CONDITION	TREATMENT	DOSE	EFFICACY ENDPOINT	CONSTIPATION TOTAL (N)	NO CONSTIPATION (N)	ABDOMINAL SYMPTOMS TOTAL (N)	ABD PAIN (N)	DIARRHEA (N)	FLATULENCE (N)	BLOATING/ABD DISTENTION (N)
Am J Gastroenterol 2012; 107:1714-1724	IBS-C	Linaclotide	PBO	≥ 3 CSBMs per week + Increase ≥ 1 CSBMs per week from baseline 9 of 12 weeks	395	25	396	10	14	6	3
		Linaclotide	290ug		405	79	406	22	79	20	9