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# **Is Lubiprostone Effective in Treating Symptoms of Chronic Constipation?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

the Degree of Masters of Science

in

Health Sciences - Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not lubiprostone is effective in treating symptoms of chronic constipation.

**STUDY DESIGN:** Review of three English language primary randomized controlled trials from 2007- 2010.

**DATA SOURCES:** Three double-blind, randomized, controlled trials were found using PubMed. These studies compared treatment with lubiprostone to a visually matched placebo.

**OUTCOME MEASURED:** The frequency of each patient's spontaneous bowel movements within the first 24 hours after initial treatment was recorded from the data collected from the patient's daily diary.

**RESULTS:** All three trials demonstrated a statistically significant improvement in the rates of spontaneous bowel movements in patients with chronic constipation receiving treatment with lubiprostone compared to those receiving the placebo.

**CONCLUSIONS:** Based on these three trials, lubiprostone is effective in treating symptoms of chronic constipation.

**KEY WORDS:** chronic constipation, lubiprostone

## INTRODUCTION

Chronic constipation is a condition that adversely affects the daily lives of many men and women. The condition is defined as less than 3 spontaneous bowel movements (SBMs) per week, in addition to symptoms of constipation associated with 25% of bowel movements over the past 6 months.<sup>1</sup> Although chronic constipation is more prevalent in the elderly population, it does affect all age groups. In the United States prevalence rates for chronic constipation range from 12–19%, with women being affected twice as often as men.<sup>2</sup> Furthermore, symptoms of constipation result in a decreased quality of life, reduced productivity and an increase in the number of missed work or school days. This leads to constipation being among one of the most frequent patient complaints faced by internists and primary care physicians, in addition to accounting for nearly 50% of referrals to gastroenterologists.<sup>1</sup>

As one of the most common digestive complaints in the general population, constipation is also associated with substantial economic costs. Each year more than 2.5 million Americans visit their healthcare provider for relief from constipation.<sup>3</sup> The estimated total medical cost of care for patients with constipation in 2001 was \$235 million per year, with 55% from inpatient care, 23% from the Emergency Department, 16% from outpatient physicians and 6% from outpatient hospital settings.<sup>4</sup> Therefore, not only is chronic constipation a burden on patients' lives, but it is taxing on the healthcare system as well.

There are many underlying causes of chronic constipation. However, the condition generally results from inadequate fiber or fluid intake, from impaired colonic transit or anorectal dysfunction.<sup>2</sup> Also, symptoms of constipation can vary from patient to patient making it difficult for practitioners to clinically quantify the severity of the condition. Symptoms generally include difficult or infrequent bowel movements, excessive straining, hard stools, lower abdominal

fullness or a sense of incomplete evacuation.<sup>2</sup> Due to the difficulty evaluating constipation, clinicians determine severity by focusing on the quantitative frequency of a patient's bowel movements via the use of patient daily dairies. The information gathered from the diary does not only help assess the degree of constipation, but can also help guide patient treatment.

There are multiple home and pharmacologic remedies for treating constipation. The initial step in treatment usually involves lifestyle and dietary modifications. Lifestyle changes include increasing fluid intake, exercising and establishing a regular bowel movement routine. Dietary changes mainly focus on increasing fiber intake. This can cause stool to bulk leading to colonic dilation that promotes intestinal peristalsis.<sup>3</sup> If lifestyle and dietary modifications fail, bulk laxatives are generally the next choice. Bulk forming laxatives include psyllium, methycellulose, polycarbophil and wheat dextrin.<sup>3</sup> These are polysaccharide or cellulose derivatives that act by absorbing water and increasing fecal mass.<sup>3</sup> If patients have no response to bulk laxatives, osmotic laxatives are the next step in treatment. Osmotic laxatives include polyethylene glycol, lactulose, sorbitol and magnesium hydroxide.<sup>3</sup> If these all fail, lubiprostone has shown considerable promise with patients suffering from chronic constipation.<sup>1</sup> As a side note, stimulant laxatives are effective in relieving acute symptoms of constipation, but should be avoided in cases of chronic constipation due to adverse affects with long term use such as dehydration and electrolyte disturbances.<sup>3</sup>

This review evaluates three double blind, randomized, controlled trials comparing the efficacy of lubiprostone in treating symptoms of chronic constipation. As previously stated, lubiprostone may be used as treatment for severe chronic constipation that is not relieved by other treatment alternatives. Lubiprostone has been shown to accelerate small intestine and colonic transit by activating chloride channels in the intestinal epithelial cells.<sup>5</sup> When activated,

these cells contribute to the secretion of intestinal fluid causing an increase in luminal water content without significantly accelerating the rate of ascending colon emptying.<sup>5</sup> This ultimately results in relief of constipation.

### **OBJECTIVE**

The objective of this systematic review is to determine whether or not lubiprostone is effective in treating symptoms of chronic constipation.

### **METHODS**

Three double-blind, randomized, controlled trials (RCTs) that included healthy men and women greater than 18 years of age with history of chronic constipation, defined as less than 3 SBMs per week, in addition to symptoms of constipation associated with 25% of bowel movements over the past 6 months were selected for study.<sup>1,5,6</sup> All three studies showed no significant differences in demographic parameters between the treatment and placebo groups. The population in each study was predominately female Caucasians with the mean age ranging between 46-48 years.<sup>1,5,6</sup> Also, the inclusion and exclusion criteria of all three studies were similar. Additionally, discontinuation rates were not substantially different between the treatment and placebo groups for each study used. These demographics and characteristics are demonstrated in Table 1. All three studies compared the experimental group, receiving treatment of lubiprostone 24mcg twice daily, to a control group, receiving a visually matched placebo. The occurrence of a SBM within the first 24 hours of the initial treatment dose was compared among experimental and control groups to determine the outcome of the studies.

All three articles used in this review were collected via PubMed database in 2014. The key words used to acquire the articles were “lubiprostone” and “constipation.” Each article used was published in English by peer reviewed journals between the years 2007 and 2010. All

articles were POEMS selected based on their outcome's relevance and importance to patients' quality of life.

The inclusion criteria were synonymous for each RCT. The defined criteria consisted of males or non-pregnant, non-lactating females over the age of 18 years old with chronic constipation.<sup>1,5,6</sup> Symptoms used to define constipation included abdominal bloating or discomfort, hard or very hard stools, sensation of incomplete evacuation or straining with defecation.<sup>1,5,6</sup> Additionally, potential participants less than 50 years old must have had a flexible sigmoidoscopy or colonoscopy performed within the last 5 years and patients over 50 years old were required to have a barium enema with flexible sigmoidoscopy or a colonoscopy to rule out organic disorders of the large bowel prior to being considered.<sup>1,5,6</sup>

Exclusion criteria were also similar for each article. The exclusion criteria consisted of documented mechanical obstruction, megacolon or a diagnosis of pseudo-obstruction. Also, known or suspected organic disorders of the large or small intestine, secondary causes of constipation, hospitalization for any gastrointestinal or abdominal surgical procedure during the 3 months prior to study initiation and any history of prior bowel resection excluded patients from participating in any of the studies.<sup>1,5,6</sup> In addition, the studies performed by Johanson et al and Johanson and Ueno excluded patients with clinically significant cardiovascular disease, liver, lung or other systemic disease.<sup>5,6</sup> Johanson et al went further to exclude patients with hematologic, urinalysis or blood chemistry abnormalities or diagnosis of cancer within the past 5 years.<sup>5</sup> Furthermore, the study by Johanson and Ueno also excluded HIV positive patients.<sup>6</sup>

Statistics were reported based on p-values using dichotomous data. A Cochran-Mantel-Haenszel test was used to adjust for a pooled center and determine if there was a consistent difference in the percentage of patients who experienced a SBM within 24 hours of initial

treatment between the experimental and control groups.<sup>1</sup> Control event rate (CER) and experimental event rate (EER) were used to calculate relative benefit increase (RBI), absolute benefit increase (ABI), relative risk increase (RRI) and absolute risk increase (ARI). ABI was then used to determine number needed to treat (NNT) and ARI was used to determine numbers needed to harm (NNH).

Table1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Barish <sup>1</sup> (2010)	RCT	237	≥18	History of chronic constipation. Constipation symptoms a/w at least 25% of BM ≥6 months. Sigmoidoscopy or colonoscopy within the last 5 years if <50yrs, required if ≥50 yrs.	Mechanical obstruction, megacolon/megarectum or a diagnosis of pseudo-obstruction. Organic disorders of the large or small intestine, secondary causes of constipation, hospitalization for any GI issue during the 3 months prior to study initiation. Prior bowel resection.	31	Lubiprostone 24 mcg capsules PO BID
Johanson <sup>5</sup> (2008)	RCT	242	≥18	Same as above inclusion criteria	Same as above exclusion criteria. Plus: Clinically significant CVS disease, liver, lung or other systemic disease. Hematologic, urinalysis or blood chemistry abnormalities or cancer within the past 5 years.	20	Lubiprostone 24 mcg capsules PO BID
Johanson <sup>6</sup> (2007)	RCT	129	18-75	Same as above inclusion criteria	Same as Johanson (2008) exclusion criteria. Plus: HIV positive.	11	Lubiprostone 24-mcg/day; 48 mcg/day; 72 mcg/day

### OUTCOMES MEASURED

Each of the three RCTs used in this review assessed the efficacy of lubiprostone on improving symptoms of chronic constipation. Patients in each study were instructed to keep a daily diary that recorded information about their bowel movements. This information included timing, straining and consistency of stools, in addition to sensations of bloating and discomfort.

Patients rated the consistency of each bowel movement using a five- point scale, with 0 equaling very loose to 4 equaling very hard. Patients also used a five- point scale to rate their degree of straining during each bowel movement, with 0 equaling no straining to 4 being very severe. Sensations of bloating and discomfort were additionally measured using a five-point scale, with 0 being absent to 4 being very severe. Furthermore, the use of any constipation relieving medication was recorded along with any adverse events.<sup>1,5,6</sup>

The daily average number of SBMs, average number of weekly SBMs and the percentage of patients experiencing a SBM on day one of treatment were calculated from the information provided in the patient diaries. The term “spontaneous bowel movement” in these cases was defined as a bowel movement occurring without the use of constipation relieving medication.<sup>1,5,6</sup> Moreover, the average level of straining during bowel movements, average stool consistency and average degree of abdominal bloating and discomfort were also measured from the information gathered from patients daily diaries. Also all adverse events were rated by the investigator based on intensity and relationship to treatment.<sup>1,5,6</sup> Although all these variables were assessed in the three RCTs, the outcome specifically looked at in this analysis is the percentage of patients experiencing a SBM within 24 hours of the initial treatment dose, which was determined based on the information reported in the patients daily dairies.

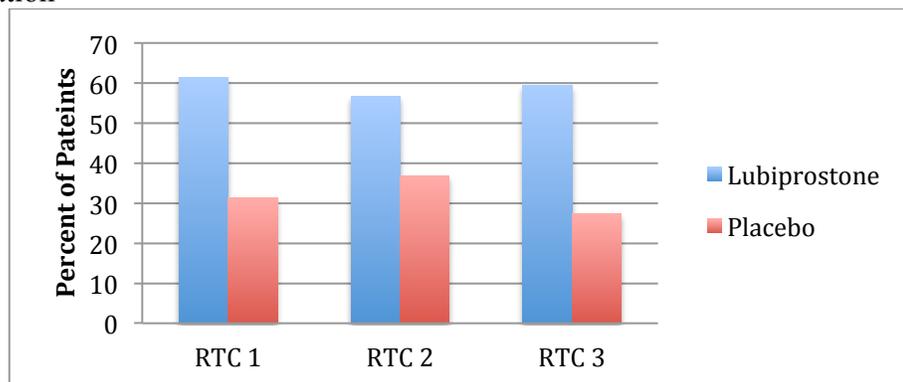
## **RESULTS**

All data from the studies used were reported as dichotomous data from which calculations evaluating tolerability, adverse events, and treatment effects were computed. Each of the RCTs looked at the efficacy of lubiprostone 24 mcg twice daily in producing a SBM within 24 hours of patients taking the initial dose compared to patients taking a placebo. All

studies were performed in outpatient settings over a 3-4 week period and relied on patients to complete their daily bowel movement diaries.

The RCT performed by Barish et al, showed that out of the 119 lubiprostone-treated patients that completed the study, 61.3% of them experienced a SBM within 24 hours of taking their first dose, compared with 31.4% of the 118 placebo treated patients that completed the study.<sup>1</sup> This data shows a significantly higher percentage of patients treated with lubiprostone having an overall shorter time to their first SBM versus the placebo patients ( $P < 0.0001$ ).<sup>1</sup> Additionally, the RCT performed by Johanson et al in 2008 showed that out of the patients that completed the study, 56.7% of the 106 lubiprostone-treated patients experienced a SBM within 24 hours of taking their first dose compared with 36.9% of the 118 placebo treated patients ( $P = 0.0024$ ).<sup>5</sup> Again this study shows a significantly higher percentage of lubiprostone treated patients having a SBM within the first 24 hours compared to the control group. Furthermore, the study by Johanson and Ueno showed that out of the 63 patients who completed the study, 59.4% of the 30 lubiprostone-treated patients experienced a SBM within 24 hours of taking their first dose compared with 27.3% of the 33 placebo treated patients ( $P = 0.009$ ).<sup>4</sup> Overall, throughout all three RCTs, the proportion of patients experiencing a SBM within the first 24 hours of the initial treatment dose was higher than that of the control group (Chart 1).

Chart 1: Percentage of patients experiencing a SBM within 24 hrs of initial dose of study medication



In the study performed by Barish et al, 72 patients experienced an SBM within 24 hours after initial treatment with lubiprostone, compared to 37 patients that were treated with the placebo. This equates to a control event rate (CER) of 31.4% and an experimental event rate (EER) of 61.3%, which yields a relative benefit increase (RBI) of 95.2% and an absolute benefit increase (ABI) of 28.9%. Using ABI, the numbers needed to treat (NNT) was calculated to be 4, meaning that a health care provider needs to treat 4 adult patients with chronic constipation with 24 mcg lubiprostone BID to have one additional patient experience a SBM within 24 hours of initial lubiprostone treatment than compared to the placebo (Table 2). Barish et al also reports that 106 patients experienced adverse effects. The reported adverse events varied from mild to moderate, but none were considered serious, with the most common being gastrointestinal in origin.<sup>1</sup> In total, 47 patients from the experimental group and 22 from the control group reported having gastrointestinal side effects. This yields a CER of 18.6% and an EER of 39.5% with a p-value of 0.0006 as determined by the Fisher exact test. The relative risk increase (RRI) was calculated to be 52.9% and the absolute risk increase (ARI) was 20.9%. Numbers needed to harm (NNH) was calculated to be 5 from the equation  $1/ARI$ , meaning for every 5 patients treated with 24 mcg lubiprostone BID, one more patient would experience an adverse event than the control (Table 3).<sup>1</sup>

Table 2: Calculations for treatment from Barish et al<sup>1</sup>

CER	EER	RBI	ABI	NNT	P-value
0.314	0.613	0.952	0.289	4	0.0003

Table 3: Calculations for harm from Barish et al<sup>1</sup>

CER	EER	RR1	ARI	NNH	P-value
0.183	0.395	0.529	0.209	5	0.0006

In the RCT performed by Johanson et al, 60 patients experienced an SBM within 24 hours after initial treatment with lubiprostone, compared to 43 patients that were treated with the placebo. This equates to a CER of 36.9% and an EER of 53.7%, which yields a RBI of 53.7%

and an ABI of 19.8%. Using ABI, the NNT was calculated to be 6 patients (Table 4). In addition, the percentage of patients experiencing one or more adverse effects was higher in the experimental group compared to the control group. For instance, 102 patients from the experimental group reported one or more adverse effects compared to 74 from the control group. This yields a CER of 50.8% and an EER of 70% with a p-value of 0.0026 as determined by the Fisher exact test. The RRI was calculated to be 37.7% and the ARI was 19.2%. NNH was calculated to be 6 patients (Table 5).<sup>5</sup>

Table 4: Calculations for treatment from Johanson et al<sup>5</sup>

CER	EER	RBI	ABI	NNT	P-vaule
0.369	0.57	0.537	0.198	6	0.0024

Table 5: Calculations for harm from Johanson et al<sup>5</sup>

CER	EER	RR1	AR1	NNH	P-vaule
0.508	0.7	0.377	0.192	6	0.0026

Lastly, in the study by Johanson and Ueno, 18 patients experienced an SBM within 24 hours after initial treatment with lubiprostone, compared to 9 patients who were treated with the placebo. This equates to a CER of 27.3% and an EER of 59.4%, which yields a RBI of 1.2% and an ABI of 32.1%. Using ABI, the NNT was calculated to be 4 patients (Table 6). In addition, the percentage of patients experiencing one or more adverse effects was higher in the experimental group compared to the control group. For instance, 24 patients from the experimental group reported one or more adverse effects compared to 13 from the control group. This yields a CER of 39% and an EER of 75%. The calculated probability or p-value for the occurrence of at least one adverse effect was determined to be 0.006 by the Cochran-Amitage test that assessed whether the adverse effect occurred at a rate related to the dose of the study drug.<sup>6</sup> The RRI was calculated to be 92% and the ARI was 36%. NNH was calculated to be 3 patients (Table 7).<sup>6</sup>

Table 6: Calculations for treatment from Johanson and Ueno

CER	EER	RBI	ABI	NNT	P-vaule
0.273	0.594	0.012	0.321	4	0.009

Table 7: Calculations for harm from Johanson et Ueno

CER	EER	RR1	AR1	NNH	P-valeur
0.39	0.75	0.92	0.36	3	0.006

In the RTC performed by Barish et al, 206 out of 237 patients completed the study. Of those, 11 patients were from the placebo group and 20 patients were from the experimental group. Of the 31 patients that discontinued the study 16 were due to adverse effects, with only one of those patients being from the placebo group. In this RCT, the adverse effects associated with lubiprostone were not serious and included nausea, upper abdominal pain, dyspnea and headache.<sup>1</sup> In the study by Johanson et al, 20 patients out of 244 discontinued, of those 14 were from the treatment group and 6 from the placebo group. The adverse effects reported were similar to those from the Barish et al study. In the Johanson et al study, adverse effects were the most common reason for discontinuation in the treatment group, whereas lack of efficacy and lost to follow up were the most common reasons in the placebo group. Of the 10 patients who discontinued due to adverse effects, only 1 patient was from the placebo group.<sup>5</sup> In the RTC by Johanson and Ureo, 9 patients discontinued the study out of 63 total patients. Of these, 2 experimental patients and 1 placebo patient were lost due to adverse effects, with the most common being nausea.<sup>6</sup> In all three studies, no clinically significant changes in laboratory values, vitals signs or physical exam findings were noted. Therefore, it does not appear that adverse effects diminish the overall tolerability of lubiprostone.<sup>1,5,6</sup>

## DISCUSSION

Based the results of the RCTs used in this review, lubiprostone 24 mcg BID significantly increases the probability of having an SBM within the first 24 hours of treatment. Each RTC analyzed produced statistically significant results with p-values less than 0.05 and without any significant outliers. This promotes the belief that lubiprostone is effective in relieving the symptoms of chronic constipation.

Despite the statistical significance of the results, there are some limitations to the RCTs used in this review. For instance, patients were advised not to change their diet or lifestyle during the studies. This could have had an underlying effect on the results depending on each patient's diet. For example, a diet high in fiber may produce different results than a diet high in refined carbohydrates or fat. Also, there was no documentation of patients' psychiatric/emotional states, such as depression, anxiety or stress, which could have affected their symptoms of constipation.

Lubiprostone is currently marketed for the treatment of chronic constipation as well as opioid induced constipation and treatment of constipation dominant irritable bowel. However, there are contraindications for its use. Lubiprostone should be avoided in patients with severe diarrhea, gastrointestinal obstructions, or patients with moderate or severe hepatic impairment. In addition, the use of methadone concurrently with lubiprostone may potentially decrease its efficacy in a dose-dependent manner.<sup>7</sup> Luckily, lubiprostone is covered by most private insurances, but only if alternative treatments have been exhausted. However, without insurance, this drug is very expensive, costing \$359.47 for a 1 month supply of lubiprostone 24 mcg BID.<sup>7</sup>

## **CONCLUSION**

The results from the three double-blind, randomized, controlled trials used in this review indicated that lubiprostone is effective in treating symptoms of chronic constipation. This conclusion was reached based on the fact that compared with those randomized to the placebo groups, patients given 24 mcg lubiprostone twice daily experienced a significantly higher number of a SBMs within the first 24 hours of initial treatment. Given the high prevalence of constipation along with decreased quality of life associated with this condition, the impact of lubiprostone on treating chronic constipation proves clinically significant.<sup>5</sup>

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