BMC Gastroenterology

RESEARCH

Open Access

Evaluation of post-market adverse events of lubiprostone: a real-world adverse event analysis from the FAERS database

Qingqing Li[1], Jijun Zhang[2], Chuanli Yang[2], Xiushan Dong[2*] and Yan Wang[3*]

Abstract

Objective Lubiprostone is a selective intestinal chloride channel activator approved for treating chronic idiopathic constipation and constipation-predominant irritable bowel syndrome in adults. However, real-world data on its long-term safety, particularly regarding adverse events necessitating ongoing supplementation, remain limited.

Methods Data from the FDA Adverse Event Reporting System (FAERS) database were collected from the second quarter of 2006 to the fourth quarter of 2023. The data was normalized, and various signal quantification techniques such as Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS) were used for analysis.

Results A total of 1436 adverse event reports associated with lubiprostone were extracted from the FAERS database. These reports indicated a higher proportion of female patients compared to male patients (65.39% vs. 21.10%). Among those with explicit age data, the largest proportion of patients were 45–65 years old (20.6% of reports), followed by those ≥ 75 (19.9%), 18–45 (14.8%), and 65–75 years (10.1%). Adverse events induced by lubiprostone were observed in 24 System Organ Classes (SOCs), including common gastrointestinal disorders, general disorders, administration site conditions, as well as respiratory, thoracic, and mediastinal disorders, consistent with findings from clinical trials. Applying four algorithms simultaneously, 22 SOC_S were detected, revealing a total of 57 positive response items, including 22 related to the digestive system. The most stringent algorithm, empirical Bayesian geometric mean (EBGM), highlighted severe gastrointestinal adverse reactions like gastric fistula ($n = 5$, ROR = 150.03, PRR = 149.87, IC = 7.21, EBGM = 147.71) and ischemic colitis ($n = 19$, ROR = 36.78, PRR = 36.63, IC = 5.19, EBGM = 36.51), which were not listed in the drug insert. This suggests the need for heightened vigilance towards these potential adverse reactions during clinical use.

Conclusions Our study comprehensively evaluated the safety of lubiprostone in the post-marketing setting. Despite its therapeutic advantages, there is a potential for various systemic adverse effects. In addition to adverse events consistent with information from existing clinical trials and the insert, we discovered several serious localized adverse reactions and previously unreported systemic adverse reactions. These may be potentially associated with

*Correspondence:
Xiushan Dong
dongxiushan2012@163.com
Yan Wang
yudiwang0917@126.com

Full list of author information is available at the end of the article

lubiprostone, but are not confirmed adverse effects. This will provide valuable evidence for future studies and further prospective clinical trials to confirm these results and elucidate the relationship between them, thus better guiding the clinical practice of lubiprostone.

Keywords Selective chloride channel agonist, Adverse events, FAERS, Real-world analysis

Introduction

Chronic idiopathic constipation (CIC) [1] is a prevalent gastrointestinal disorder, with a global prevalence of 14% as evidenced by a population-based meta-analysis of 45 projects. This prevalence shows little geographic variation, with a higher occurrence in women and an increase with age [1, 2]. Irritable bowel syndrome (IBS) is another functional gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits, including constipated, mixed, and non-directed types [3]. Both CIC and IBS significantly impact an individual's quality of life, healthcare costs, and societal economic burden. There is often overlap between the two conditions, with patients experiencing changes in primary symptoms and potential transitions between the diseases over time and in response to treatment [4].

The pathophysiology of CIC and constipation-predominant irritable bowel syndrome with constipation (IBS-C) is intricate and not fully understood. Genetics, diet, psychosocial factors, and the gut microbiome are all acknowledged as risk factors, but their roles may vary depending on geography and culture, leading to differences in relative importance across countries [5]. Lifestyle modifications, such as increasing dietary fiber and fluid intake, along with behavioral changes, are typically the initial steps in managing constipation. While conventional laxatives are commonly used as a first-line pharmacologic treatment, many patients continue to experience dissatisfaction with symptom relief. The introduction of pro-secretory agents like lubiprostone has brought about significant advancements in clinical research for both conditions, becoming a crucial component in the therapeutic management of CIC and IBS-C [6]. A systematic review of nine trials involving 1,468 patients in the lubiprostone group and 841 patients in the placebo group demonstrated significant improvements in constipation, stool consistency, abdominal pain, straining, and bloating at 1 week and 1 month, with sustained improvement in bloating at 3 months [7]. Results from a phase III study indicated that lubiprostone not only increased spontaneous bowel movements in CIC patients but also enhanced their quality of life [8]. Early safety studies of lubiprostone revealed adverse reaction rates ranging from 2.4 to 75%, with serious adverse reactions occurring in less than 5% of cases across different studies [7]. In addition to common gastrointestinal side effects like nausea, vomiting, and diarrhea, systemic adverse reactions such as headaches have also been noted [9]. Lubiprostone has been marketed in Europe, Japan, and China in recent years. The approved inserts vary in content between countries, particularly in the description of adverse reactions, and there is a lack of comprehensive safety studies on a larger scale [10]. With the increasing use of lubiprostone in clinical settings, new potential adverse reactions may come to light. Furthermore, the limited patient pool and short follow-up periods in single-center clinical studies may hinder a thorough evaluation of the drug's safety profile.

This study conducted a comprehensive marketed ADR revaluation of lubiprostone by analyzing and updating its safety risks using the FAERS database. It identified potential adverse events that require special attention to support more prudent drug decision-making and provide guidance for clinical practice, aiming to improve clinical drug use and treatment.

Methods

Data sources

American Standard Code for Information Interchange (ASCII) report files from the FAERS database were downloaded for the period spanning from the second quarter of 2006 to the fourth quarter of 2023. The data was imported into MySQL 15.0 and processed using Navicat Premium 15 software.

Data extraction

The data extraction process initially utilized the Medex_UIMA 1.8.3 system to standardize drug names, ensuring consistent identification of all cases involving lubiprostone. We extracted all reports identifying lubiprostone as the primary suspect drug and excluded cases where lubiprostone was listed as a secondary or concomitant medication without a clear association with the reported adverse events. To clean the dataset, we adhered to FDA-recommended criteria for eliminating duplicate reports: for reports with identical CASEIDs, only the one with the most recent FDA_DT (date of receipt) was retained. In cases where CASEIDs and FDA_DTs were identical, we retained the report with the highest PRIMARYID. Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA), which categorizes them into SOCs and Preferred Terms (PTs). The version of MedDRA used in this study was the most current at the time of data extraction. The final dataset encompassed all adverse event reports associated with lubiprostone during the study period. We compiled

clinical characteristics such as patient age, gender, and reporting region, as well as patient outcomes. The specific analysis process is shown in Fig. 1.

Signal analysis

This study utilized four methods for AEs signal mining, including the ROR [11] method, the PRR [12] method, BCPNN [13] method, and MGPS [14] method, and the predefined thresholds for signal detection are ROR ≥ 3, 95% CI (lower limit) > 1; PRR ≥ 2, 95% CI (lower limit) > 1; IC025 > 0; EBGM05 > 2. By leveraging the strengths of each method, we aimed to broaden detection capabilities, validate results from diverse perspectives, and effectively utilize the unique features of different algorithms to identify comprehensive and reliable safety signals. Employing multiple algorithms in combination facilitated cross-validation to minimize false positives, enabling the detection of potentially rare adverse effects through threshold and variance adjustments.

Statistical analysis was conducted using R software (version 4.1.3), with higher values indicating stronger signal strength and a more robust association between the target drug and the AE.

Results

Basic characteristics of lubiprostone AEs

A total of 19,421,549 adverse event reports were collected from the FAERS database for this study, spanning from the second quarter of 2006 to the fourth quarter of 2023. Among these reports, lubiprostone was identified as the primary suspected adverse drug event in 1,436 cases. The adverse event reports for lubiprostone showed a higher proportion of female patients compared to male patients (65.39% vs. 21.10%).

In terms of age, 32.94% of reports did not include age information. Among reports with explicit age data, the largest proportion of patients were 45–65 years old (20.6% of reports), followed by those ≥ 75 (19.9%), 18–45 (14.8%), and 65–75 years (10.1%), and a very small percentage, 1.67%, were younger than 18 years. The majority of reports were from healthcare workers (55.71%) and consumers (35.65%). The highest number of reports came from Japan (35.24%) and the United States (29.81%).

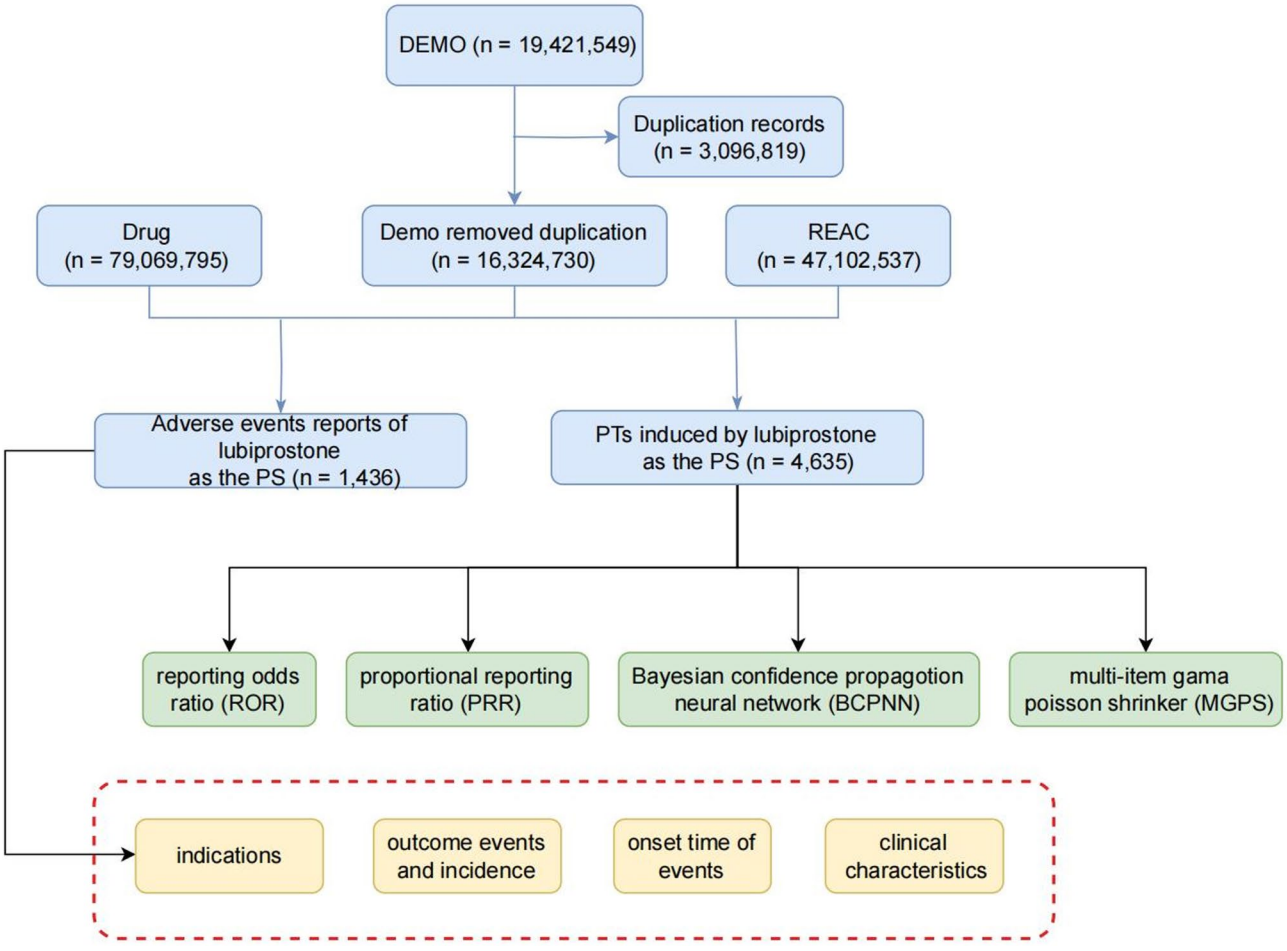

Fig. 1 The flowchart of selecting lubiprostone-related AEs from FAERS database

Regarding clinical outcomes, adverse events leading to hospitalization were the most common (30.97%), followed by death (6.33%), excluding unspecified serious adverse events. More details can be found in Table 1. The number of lubiprostone-related adverse events reported per year can be seen in Fig. 2.

Signals of system organ class

In this study, adverse event reports involving lubiprostone were analyzed, identifying 24 SOCs for adverse reactions associated with the drug. The results, detailed in Table 2, revealed that the most common systems affected were gastrointestinal disorders ($n = 1074$, ROR 3.07, PRR 2.59, IC 1.37, EBGM 2.59), general disorders and administration site conditions ($n = 857$, ROR 1.01, PRR 1.01, IC 0.02, EBGM 1.01), and respiratory, thoracic, and mediastinal disorders ($n = 514$, ROR 2.38, PRR 2.23, IC 1.16, EBGM 2.23). In addition, neurologic disorders ($n = 453$, ROR 1.11, PRR 1.1, IC 0.14, EBGM 1.1) and metabolic and nutritional disorders ($n = 188$, ROR 1.84, PRR 1.81, IC 0.85, EBGM 1.81) should also be of particular concern because of the high number of reports of these adverse reactions and their positive signals.

Table 1 Basic information on AEs related to Lubiprostone from the FAERS database

Variable	Total *N* (%)
Sex	
Female	939 (65.39)
Male	303 (21.10)
Unkown	194 (13.51)
Age group	
< 18	24 (1.67)
18–45	213 (14.83)
45–65	296 (20.61)
65–75	145 (10.10)
≥ 75	285 (19.85)
Unknown	473 (32.94)
Reporter	
Consumer	512 (35.65)
Physician	438 (30.50)
Pharmacist	197 (13.72)
Other health-professional	161 (11.21)
Unkown	122 (8.50)
Registered Nurse	4 (0.28)
Lawyer	2 (0.14)
Reported countries	
Japan	506 (35.24)
United States	428 (29.81)
Other	502 (34.96)
Outcomes	
Hospitalization	328 (30.97)
Death	67 (6.33)
Life threatening	37 (3.49)
Disability	24 (2.27)
Required intervention to Prevent Permanent Impairment/Damage	9 (0.85)
Congenital anomaly	2 (0.19)
Unknown	592 (55.90)
Time to onset	
< 7	466 (46.74)
7–28	104 (10.43)
28–60	41 (4.11)
≥ 60	81 (8.12)
Unknown	305 (30.59)

Signal detection at PT level

In the study, 57 PTs meeting the criteria were screened using four algorithms at the Preferred Term level. Among them, 22 PTs were associated with gastrointestinal adverse reactions. The gastrointestinal adverse reactions were ranked by signal intensity, Gastric fistula, rectal tenesmus, and ischemic colitis were listed as the top 3 signal intensity adverse reactions in all 4 methods, as detailed in Table 3. In terms of frequency, the most common PTs were nausea ($n = 192$), diarrhea ($n = 164$), and flatulence ($n = 91$). Additionally, there were 15 SOCs and 35 PTs related to other systemic adverse reactions. The SOCs with the highest number of adverse reactions were respiratory, thoracic and mediastinal disorders, and neurologic disorders. The top three PTs in this category were dyspnea, chest discomfort, and chest pain. PTs with the strongest signal intensity were ranked using the EBGM algorithm, with clubbing ($n = 3$, ROR = 91.6, PRR = 266.27, IC = 6.5, EBGM = 90.74), cerebral palsy ($n = 3$, ROR = 39.72, PRR = 112.72, IC = 5.31, EBGM = 39.54), and metabolic alkalosis ($n = 4$, ROR = 32.81, PRR = 122.72, IC = 5.03, EBGM = 32.68) being highlighted (Table 4). Cerebral palsy may be a potential artifact or misinterpretation because it is not a reasonable adverse effect of constipating medications and because the known risks of lubiprostone are concentrated in the gastrointestinal tract, with minimal systemic absorption, and there is no evidence of an association with cerebral palsy. So these signals require further epidemiologic or mechanistic studies.

Analysis of gender differences

Subgroup analysis revealed gender-specific differences in lubiprostone-associated high-risk AEs: females were primarily characterized by dyspnea, chest pain, and chest discomfort, while males were mainly associated with dyspnea, diarrhea, and chest discomfort. Notably, dyspnea and chest discomfort emerged as common high-risk AEs shared by both genders (Fig. 3).

Analysis of age differences

Subgroup analysis revealed age-stratified patterns in lubiprostone-associated high-risk AEs. Chest discomfort

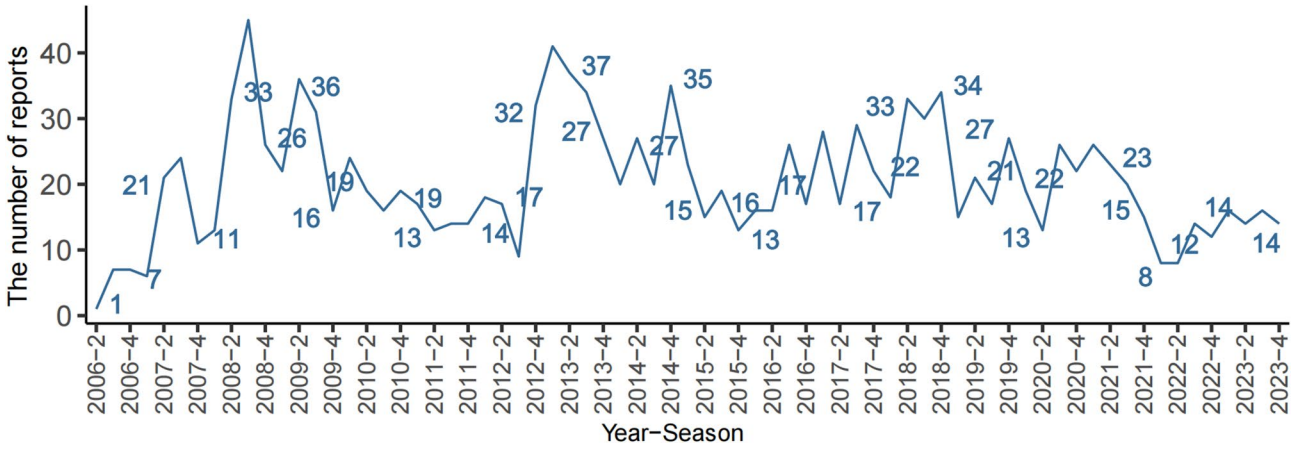

Fig. 2 Reported years of AEs associated with lubiprostone in the FAERS database

Table 2 The signal strength of AEs of Lubiprostone at the SOCs level in FAERS database

SOCs	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Gastrointestinal disorders	1074	3.07 (2.87, 3.29)	2.59 (2.44, 2.75)	1.37 (1.28)	2.59 (2.45)
Respiratory, thoracic and mediastinal disorders	514	2.38 (2.18, 2.61)	2.23 (2.06, 2.41)	1.16 (1.03)	2.23 (2.07)
Metabolism and nutrition disorders	188	1.84 (1.59, 2.13)	1.81 (1.58, 2.08)	0.85 (0.64)	1.81 (1.60)
Nervous system disorders	453	1.11 (1.01, 1.23)	1.10 (1.02, 1.19)	0.14 (0)	1.1 (1.02)
Hepatobiliary disorders	44	1.02 (0.75, 1.37)	1.02 (0.76, 1.37)	0.02 (-0.40)	1.02 (0.79)
General disorders and administration site conditions	857	1.01 (0.94, 1.09)	1.01 (0.95, 1.07)	0.02 (-0.09)	1.01 (0.95)
Cardiac disorders	122	0.97 (0.81, 1.16)	0.97 (0.81, 1.16)	-0.05 (-0.30)	0.97 (0.83)
Investigations	282	0.95 (0.85, 1.08)	0.96 (0.85, 1.08)	-0.06 (-0.24)	0.96 (0.87)
Immune system disorders	51	0.95 (0.72, 1.25)	0.95 (0.72, 1.25)	-0.08 (-0.47)	0.95 (0.75)
Ear and labyrinth disorders	18	0.86 (0.54, 1.37)	0.86 (0.54, 1.38)	-0.21 (-0.86)	0.86 (0.58)
Vascular disorders	90	0.86 (0.7, 1.06)	0.86 (0.71, 1.05)	-0.21 (-0.51)	0.86 (0.72)
Pregnancy, puerperium and perinatal conditions	17	0.82 (0.51, 1.32)	0.82 (0.51, 1.31)	-0.29 (-0.96)	0.82 (0.55)
Renal and urinary disorders	70	0.77 (0.61, 0.98)	0.78 (0.62, 0.99)	-0.36 (-0.70)	0.78 (0.64)
Endocrine disorders	8	0.66 (0.33, 1.31)	0.66 (0.33, 1.31)	-0.61 (-1.55)	0.66 (0.37)
Musculoskeletal and connective tissue disorders	158	0.6 (0.51, 0.70)	0.61 (0.52, 0.71)	-0.71 (-0.94)	0.61 (0.54)
Psychiatric disorders	133	0.46 (0.39, 0.55)	0.48 (0.40, 0.57)	-1.06 (-1.31)	0.48 (0.41)
Skin and subcutaneous tissue disorders	124	0.46 (0.39, 0.55)	0.48 (0.40, 0.57)	-1.07 (-1.33)	0.48 (0.41)
Injury, poisoning and procedural complications	207	0.44 (0.38, 0.51)	0.47 (0.41, 0.54)	-1.1 (-1.30)	0.47 (0.41)
Eye disorders	42	0.43 (0.32, 0.58)	0.43 (0.32, 0.58)	-1.2 (-1.64)	0.43 (0.34)
Congenital, familial and genetic disorders	6	0.4 (0.18, 0.88)	0.4 (0.18, 0.89)	-1.33 (-2.40)	0.40 (0.20)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	48	0.35 (0.27, 0.47)	0.36 (0.27, 0.47)	-1.47 (-1.87)	0.36 (0.29)
Infections and infestations	93	0.35 (0.29, 0.43)	0.37 (0.30, 0.45)	-1.45 (-1.75)	0.37 (0.31)
Reproductive system and breast disorders	14	0.34 (0.20, 0.58)	0.35 (0.21, 0.59)	-1.53 (-2.26)	0.35 (0.22)
Blood and lymphatic system disorders	22	0.27 (0.18, 0.41)	0.27 (0.18, 0.41)	-1.88 (-2.48)	0.27 (0.19)

consistently emerged across all age groups as the predominant AE. Younger patients (< 18 years) exhibited chest pain and dyspnea alongside chest discomfort, while adults aged 18–45 years showed a distinct association with nausea. Middle-aged individuals (45–65 years) demonstrated recurrent chest pain combined with persistent dyspnea and chest discomfort. In older populations, gastrointestinal symptoms predominated: abdominal distension and diarrhea characterized the 65–75 age group, whereas those ≥ 75 years displayed diarrhea and nausea, with chest discomfort remaining prevalent. This age-dependent transition highlights chest discomfort as a universal risk and identifies gastrointestinal manifestations as a critical concern in elderly patients (Fig. 4).

Discussion

Lubiprostone, a bicyclic fatty acid derived from prostaglandin E1, functions by enhancing intestinal chloride secretion through the activation of type 2 chloride channels on epithelial cells. This mechanism leads to an

Table 3 Ranked the GI adverse effects of Lubiprostone according to ROR

PT	Case reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Gastric fistula	5	150.03 (62.02, 362.96)	149.87 (62.04, 362.04)	7.21 (6.04)	147.71 (70.53)
Rectal tenesmus	4	45.97 (17.21, 122.80)	45.93 (17.24, 122.38)	5.51 (4.25)	45.72 (20.09)
Colitis ischaemic	19	36.78 (23.42, 57.77)	36.63 (23.34, 57.49)	5.19 (4.56)	36.51 (25.02)
Faecaloma	14	34.41 (20.35, 58.20)	34.31 (20.21, 58.24)	5.1 (4.36)	34.2 (22.03)
Gastrointestinal hypomotility	4	33.26 (12.46, 88.80)	33.23 (12.47, 88.54)	5.05 (3.78)	33.13 (14.57)
Gastrointestinal oedema	4	28.85 (10.81, 77.01)	28.83 (10.82, 76.82)	4.85 (3.58)	28.75 (12.64)
Volvulus	5	27.87 (11.58, 67.07)	27.84 (11.52, 67.25)	4.8 (3.64)	27.77 (13.32)
Faeces hard	6	20.64 (9.26, 46.01)	20.62 (9.23, 46.06)	4.36 (3.29)	20.58 (10.52)
Infrequent bowel movements	3	15.3 (4.93, 47.51)	15.3 (4.91, 47.69)	3.93 (2.52)	15.27 (5.92)
Bowel movement irregularity	5	8.48 (3.53, 20.39)	8.47 (3.51, 20.46)	3.08 (1.93)	8.46 (4.06)
Defaecation urgency	4	8.23 (3.09, 21.95)	8.23 (3.09, 21.93)	3.04 (1.77)	8.22 (3.62)
Intestinal obstruction	38	7.99 (5.81, 11.00)	7.93 (5.80, 10.85)	2.99 (2.53)	7.93 (6.07)
Abnormal faeces	5	7.73 (3.22, 18.59)	7.72 (3.2, 18.65)	2.95 (1.79)	7.72 (3.71)
Flatulence	91	7.3 (5.93, 8.98)	7.17 (5.89, 8.72)	2.84 (2.54)	7.17 (6.03)
Intestinal ischaemia	3	6.99 (2.25, 21.68)	6.98 (2.24, 21.76)	2.8 (1.39)	6.98 (2.71)
Anorectal discomfort	3	6.27 (2.02, 19.45)	6.27 (2.01, 19.54)	2.65 (1.23)	6.26 (2.43)
Anal incontinence	4	6.12 (2.30, 16.33)	6.12 (2.30, 16.31)	2.61 (1.35)	6.12 (2.69)
Haemorrhoids	9	5.64 (2.93, 10.86)	5.64 (2.95, 10.77)	2.49 (1.60)	5.63 (3.26)
Constipation	56	3.35 (2.58, 4.37)	3.33 (2.58, 4.30)	1.73 (1.36)	3.32 (2.67)
Diarrhoea	164	3.31 (2.83, 3.87)	3.23 (2.76, 3.78)	1.69 (1.47)	3.23 (2.83)
Gastrointestinal pain	63	3.28 (2.56, 4.21)	3.25 (2.52, 4.19)	1.7 (1.34)	3.25 (2.64)
Nausea	192	3.14 (2.71, 3.62)	3.05 (2.66, 3.50)	1.61 (1.40)	3.05 (2.70)

increase in intestinal fluid secretion, subsequently promoting intestinal peristalsis. As a result, lubiprostone aids in fecal elimination and alleviates symptoms commonly associated with CIC, such as abdominal pain, discomfort, and bloating. It has been approved by the FDA for the treatment of CIC at a dosage of 24 mg twice daily, and for IBS-C at a dosage of 8 mg twice daily [6].

As a novel agent for treating CIC and IBS-C, lubiprostone shows promising therapeutic and safety advantages. Initial research has indicated that adverse reactions like nausea, vomiting, and diarrhea are more prevalent, while systemic and severe adverse reactions are less frequent. Nevertheless, data on adverse reactions are still scarce, and typical adverse reactions at different locations have not been pinpointed. Therefore, it is imperative to closely monitor both the actual utilization of the product and any adverse events that may arise. Post-marketing surveillance is crucial in uncovering potential safety concerns in real-world clinical settings, and spontaneous reporting systems offer valuable opportunities to enhance the current understanding through additional evidence.

This study systematically evaluated the adverse reactions associated with lubiprostone by conducting an extensive analysis of the FAERS database spanning from the second quarter of 2006 to the fourth quarter of 2023. We systematically compared the coincidence of FAERS findings with the specification and adverse reactions in relevant reports to assess their consistency.Through this investigation, the study not only confirmed existing safety information but also uncovered new potential risks. Adverse event reports involving lubiprostone were more prevalent in female patients compared to male patients, possibly attributed to the FDA-approved indication being limited to females over 18 years of age and their higher frequency of drug intake [15]. The study reaffirmed that the most common gastrointestinal adverse reactions were nausea ($n = 192$, ROR = 3.14, PRR = 3.05, IC = 1.61, EBGM = 3.05), diarrhea ($n = 164$, ROR = 3.31, PRR = 3.23, IC = 1.69, EBGM = 3.23), and flatulence ($n = 91$, ROR = 7.3, PRR = 7.17, IC = 2.84, EBGM = 6.03). Furthermore, more severe adverse reactions such as gastric fistula ($n = 5$, ROR = 150.03, PRR = 149.87, IC = 7.21, EBGM = 147.71), ischemic colitis ($n = 19$, ROR = 36.78, PRR = 36.63, IC = 5.19, EBGM = 36.51), clubbing ($n = 3$, ROR = 91.6, PRR = 91.53, IC = 6.5, EBGM = 90.74)and other adverse events were also identified. Although the number of examples is small, there is a strong signal in all four methods of analysis.

Gastrointestinal-related AEs

Gastrointestinal adverse effects of lubiprostone showed a clear dose-dependency, and in the treatment of CIC, the high dose regimen of 24 mg twice daily (BID) led to a significantly higher risk of AEs: the short-term phase III trial showed that 39.5% of the patients reported gastrointestinal AEs (vs. 18.6% in the placebo group), of which 24.4% were nausea (vs. 6.8%) [16]; during 48 weeks of long-term treatment, 19.8% of patients experienced

Table 4 PTs of other SOCs in Lubiprostone sorted by EBGM

SOCs	PTs	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Musculoskeletal and connective tissue disorders	Clubbing	3	91.60 (29.38, 285.58)	91.54 (29.37, 285.31)	6.5 (5.08)	90.74 (35.04)
Congenital, familial and genetic disorders	cerebral palsy	3	39.72 (12.78, 123.47)	39.69 (12.73, 123.7)	5.31 (3.89)	39.54 (15.31)
Metabolism and nutrition disorders	metabolic alkalosis	4	32.81 (12.29, 87.59)	32.78 (12.3, 87.34)	5.03 (3.76)	32.68 (14.37)
General disorders and administration site conditions	physical deconditioning	3	22.23 (7.16, 69.05)	22.22 (7.13, 69.25)	4.47 (3.05)	22.17 (8.59)
Infections and infestations	enteritis infectious	3	20.84 (6.71, 64.7)	20.82 (6.68, 64.89)	4.38 (2.96)	20.78 (8.05)
General disorders and administration site conditions	chest discomfort	154	19.86 (16.91, 23.33)	19.24 (16.45, 22.51)	4.26 (4.03)	19.2 (16.79)
General disorders and administration site conditions	drug tolerance	7	17.6 (8.38, 36.96)	17.57 (8.34, 37)	4.13 (3.13)	17.54 (9.43)
Immune system disorders	anaphylactoid reaction	5	15.81 (6.57, 38.04)	15.8 (6.54, 38.17)	3.98 (2.82)	15.78 (7.57)
Respiratory, thoracic and mediastinal disorders	choking sensation	6	13.68 (6.14, 30.48)	13.66 (6.12, 30.51)	3.77 (2.7)	13.65 (6.98)
Injury, poisoning and procedural complications	face injury	3	10.16 (3.27, 31.54)	10.16 (3.26, 31.67)	3.34 (1.93)	10.15 (3.93)
Skin and subcutaneous tissue disorders	skin odour abnormal	3	9.51 (3.06, 29.51)	9.5 (3.05, 29.61)	3.25 (1.83)	9.49 (3.68)
Psychiatric disorders	autism spectrum disorder	3	9.27 (2.99, 28.78)	9.27 (2.97, 28.89)	3.21 (1.8)	9.26 (3.59)
Nervous system disorders	altered state of consciousness	15	8.78 (5.29, 14.58)	8.75 (5.26, 14.57)	3.13 (2.42)	8.75 (5.72)
Eye disorders	abnormal sensation in eye	3	8.54 (2.75, 26.51)	8.54 (2.74, 26.62)	3.09 (1.68)	8.53 (3.31)
Skin and subcutaneous tissue disorders	cold sweat	11	7.78 (4.31, 14.07)	7.77 (4.32, 13.99)	2.96 (2.14)	7.76 (4.73)
Pregnancy, puerperium and perinatal conditions	pregnancy	12	7.67 (4.35, 13.53)	7.66 (4.34, 13.52)	2.94 (2.15)	7.65 (4.76)
Respiratory, thoracic and mediastinal disorders	pharyngeal oedema	11	7.59 (4.2, 13.72)	7.58 (4.21, 13.65)	2.92 (2.1)	7.57 (4.61)
Respiratory, thoracic and mediastinal disorders	dyspnoea	333	7.81 (6.99, 8.73)	7.32 (6.64, 8.07)	2.87 (2.71)	7.32 (6.67)
Respiratory, thoracic and mediastinal disorders	throat tightness	15	6.98 (4.2, 11.59)	6.96 (4.18, 11.59)	2.8 (2.09)	6.95 (4.55)
Metabolism and nutrition disorders	electrolyte imbalance	40	6.80 (4.98, 9.29)	6.75 (4.93, 9.24)	2.75 (2.31)	6.75 (5.20)
Investigations	blood albumin decreased	4	6.62 (2.48, 17.64)	6.61 (2.48, 17.61)	2.72 (1.46)	6.61 (2.91)
Respiratory, thoracic and mediastinal disorders	hyperventilation	3	6.42 (2.07, 19.91)	6.41 (2.06, 19.98)	2.68 (1.27)	6.41 (2.49)
General disorders and administration site conditions	chest pain	86	5.9 (4.76, 7.3)	5.81 (4.68, 7.21)	2.54 (2.23)	5.8 (4.85)
Investigations	blood pressure decreased	26	4.99 (3.4, 7.34)	4.97 (3.36, 7.36)	2.31 (1.77)	4.97 (3.60)
Nervous system disorders	syncope	40	4.96 (3.64, 6.78)	4.93 (3.6, 6.75)	2.3 (1.86)	4.93 (3.80)
Nervous system disorders	parkinson's disease	7	4.69 (2.24, 9.85)	4.69 (2.23, 9.88)	2.23 (1.23)	4.69 (2.52)
Hepatobiliary disorders	drug-induced liver injury	10	4.7 (2.53, 8.74)	4.69 (2.5, 8.78)	2.23 (1.38)	4.69 (2.79)
Hepatobiliary disorders	hepatic function abnormal	13	4.67 (2.71, 8.04)	4.65 (2.69, 8.05)	2.22 (1.46)	4.65 (2.95)

Table 4 (continued)

SOCs	PTs	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	presyncope	9	4.54 (2.36, 8.72)	4.53 (2.37, 8.65)	2.18 (1.28)	4.53 (2.62)
Cardiac disorders	palpitations	40	4.29 (3.14, 5.85)	4.26 (3.11, 5.83)	2.09 (1.65)	4.26 (3.28)
Metabolism and nutrition disorders	feeding disorder	6	4.25 (1.91, 9.47)	4.25 (1.9, 9.49)	2.09 (1.02)	4.24 (2.17)
Metabolism and nutrition disorders	dehydration	44	4.13 (3.07, 5.56)	4.1 (3.06, 5.5)	2.04 (1.61)	4.1 (3.20)
Infections and infestations	diverticulitis	8	3.62 (1.81, 7.25)	3.62 (1.82, 7.19)	1.86 (0.91)	3.62 (2.03)
Nervous system disorders	loss of consciousness	34	3.37 (2.41, 4.73)	3.36 (2.41, 4.69)	1.75 (1.27)	3.36 (2.53)
Investigations	heart rate increased	24	3.11 (2.08, 4.64)	3.1 (2.09, 4.59)	1.63 (1.06)	3.09 (2.21)

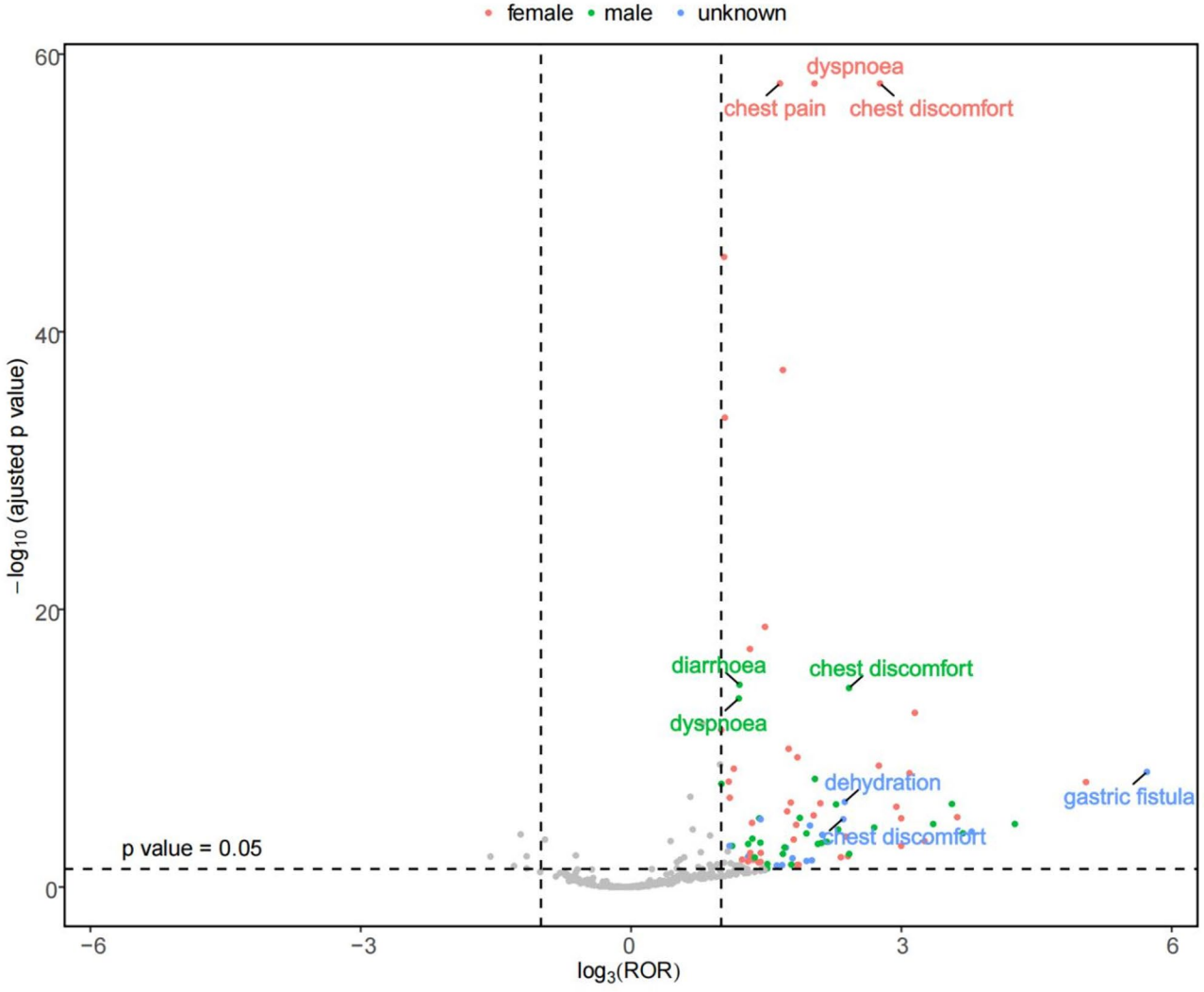

Fig. 3 Comparison of both sex safety signals of lubiprostone

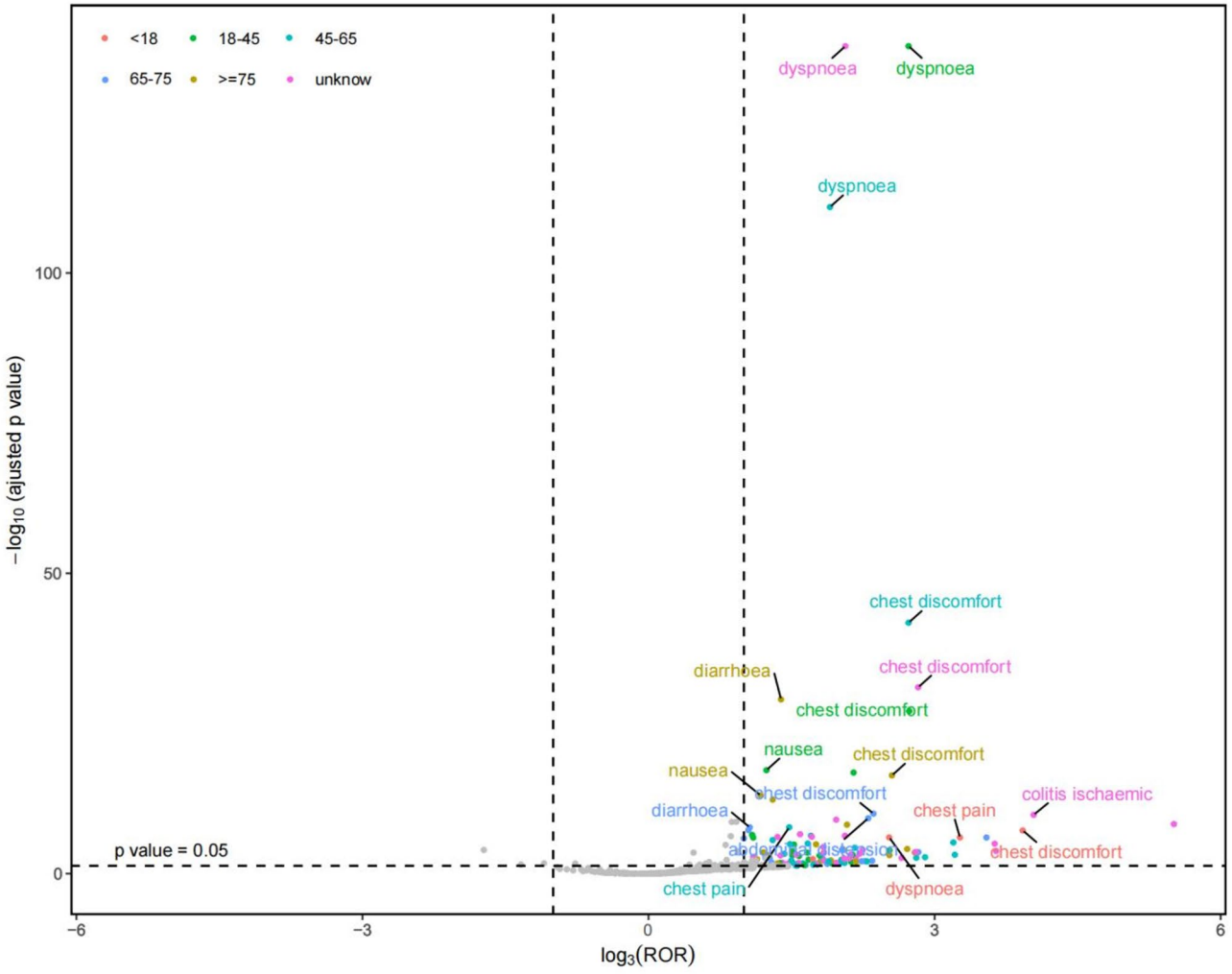

Fig. 4 Comparison of lubiprostone-associated safety signals across different age groups

nausea and 9.8% diarrhea, of which 5.2% withdrew from the study due to nausea. In contrast, the incidence of gastrointestinal AEs was significantly lower in IBS-C with a low dose of 8 μg BID, including diarrhea (6.5%), nausea (6.3%), abdominal distension (3.7%), abdominal pain (2.9%), gastrointestinal gas and bloating (2.1%), epigastric pain (1.9%), and vomiting (1.2%). Only 4% of patients discontinued the drug due to AEs and no serious AEs were drug-related [17]. This discrepancy may stem from the fact that the visceral hypersensitivity state of IBS-C patients masks the pro-secretory effects, whereas CIC patients are more sensitive to high doses due to chronic intestinal dyskinesia. In addition, the cumulative risks of long-term dosing need to be guarded against: 13.3% of CIC patients discontinued due to AEs in 48 weeks of treatment [18] In the future, balancing efficacy and safety through stepwise dose titration (e.g., starting from 8 mg BID for CIC), as well as exploring biomarker (e.g., plasma PGE2)-guided individualized strategies, are needed to break through the current symptom-driven dependency limitations.

Ischemic colitis-related and gastric fistula-related AEs

There have been no strong signals of ischemic colitis since its introduction in 2006, and only this one case confirmed to be due to lubiprostone has been reported. Muhammed Sherid first reported ischemic colitis caused by lubiprostone, confirming a clear association with lubiprostone (Naranjo score of 10) [19]. Possible mechanisms leading to ischemic colitis include: (1). Rapid fluid transfer leading to local hypoperfusion, lubiprostone activates chloride channels (CLC-2) in the parietal membranes of intestinal epithelial cells and promotes the secretion of chloride, sodium, and water into the intestinal lumen, resulting in a dramatic increase in the amount of fluid in the intestinal lumen. This rapid fluid transfer may cause a decrease in local blood volume in the intestinal tract, especially in patients with pre-existing vascular pathologies (e.g., diabetes mellitus, hypertension), which may

induce ischemic colitis. (2). Elevated luminal pressure and large amounts of fluid secretion may increase the pressure in the lumen of the intestinal tract, which may compress the blood vessels of the intestinal wall (especially in the "watershed" area of the colon) and obstruct the blood flow, impeding blood flow and leading to mucosal ischemia [20]. (3). Direct vasoconstriction, lubiprostone, as a prostaglandin E1 derivative, may cause vasoconstriction through stimulation of prostaglandin receptors (e.g., EP receptors) [21], which further reduces intestinal blood flow. (4). Synergistic effect of underlying disease and chronic constipation, chronic constipation itself may increase intestinal luminal pressure or affect intestinal blood flow, which studies have shown to increase the risk of ischemic colitis by 2.7-fold [22]. The FAERS database received five reports of gastric fistula associated with lubiprostone use. Although the exact mechanism underlying lubiprostone-associated gastric fistula formation remains unclear, the drug's prokinetic effects—characterized by increased gastrointestinal motility and accelerated transit time, may elevate perforation risks in patients with compromised gastrointestinal integrity [23].

Clubbing-related AEs

In this study, a significant association between clubbing and lubiprostone was detected by four pharmacovigilance analysis methods ($n = 3$, ROR 91.6, PRR 91.53, IC 6.5, EBGM 90.74), suggesting the need to be alerted to the clinical risk of clubbing as an adverse drug reaction. clubbing as a classical clinical sign was firstly recorded by Hippocrates, it is characterized by painless enlargement of the distal phalanx and abnormal nail morphology, including (1) a skin-nail base angle of $>180°$ at the end of the finger; (2) disappearance of the rhombic window formed by the dorsal aspect of the adjacent phalanx; and (3) pathologically visible capillary dilatation, interstitial edema, and vascular smooth muscle proliferation [24]. Notably, the pathogenesis is closely related to the persistent elevation of prostaglandin E2 (PGE2), a potent vasodilator that activates persistent vasodilatation of the distal phalanx and an imbalance in osteogenic/osteoclastic activity, leading to characteristic bone remodeling (periosteal hyperplasia and trabecular lysis). lubiprostone, a bicyclic fatty acid derivative of prostaglandin E, has been shown to be an important component in the pathogenesis of prostaglandin E2 [25]. fatty acid prostaglandin E derivative, its pharmacological effects are not limited to ClC-2 channel activation. In vitro studies have demonstrated that it significantly activates the PGEP1 receptor (mediating 54% of maximal PGE2 activity), affecting inflammation, cell proliferation, and vascular function by modulating transmembrane signaling pathways. This property may be directly related to its ability to induce adverse effects of clubbing. Clinical cases further support this hypothesis: Kawamoto et al. reported a case of a patient on long-term lubiprostone use with a significantly elevated urinary PGE2/creatinine ratio (2.8-fold increase from baseline) and complete resolution of clubbing symptoms after 3 months of discontinuation with normalization of PGE2 levels [26]. This temporal correlation of "medication-biomarker change-symptom relief" strongly suggests that lubiprostone may drive clubbing by upregulating PGE2 levels.

Dyspnea - related AEs

Subgroup analyses identified dyspnea as an adverse reaction across genders and younger age groups in lubiprostone-treated patients. Theoretically, lubiprostone exhibits poor absorption from the gut and low systemic bioavailability following oral administration, resulting in extremely low and unmeasured blood concentrations of the prototype drug (less than 10 pg/mL) [27] Post-marketing surveillance has revealed systemic adverse reactions, including dyspnea. This paradox may stem from its active metabolite M3, generated via rapid metabolism of the prototype drug by microsomal carbonyl reductase in the stomach and jejunum. M3 demonstrates high binding affinity to human plasma proteins following absorption. Metabolites of lubiprostone have been shown to stimulate cystic fibrosis transmembrane conductance regulator (CFTR)-dependent airway secretion and non-CFTR-dependent respiratory epithelial secretion from tracheal submucosal glands, potentially explaining the rare occurrence of dyspnea associated with lubiprostone use [28].

Cardiovascular events-related AEs

In a large national cohort study of more than 3 million United States veterans, Keiichi Sumida et al. found that constipation status and laxative use were associated with an increased risk of all-cause mortality, new coronary heart disease, and new ischemic stroke, independent of known cardiovascular risk factors. They suggested that dehydration induced by certain types of laxatives, as well as recurrent Valsalva-like apnea due to straining to defecate, was an important cause of "defecatory syncope", which may lead to cardiac and cerebral ischemia and thus may explain the higher incidence of cardiovascular events [29]. Wenyu Zhang et al. found 22 case reports of palpitations and 17 case reports of increased heart rate due to the administration of lubiprostone, which were not mentioned in the specification [30]. Emanuel Raschi et al. found that chest discomfort or chest pain were present in 32% of cases, and they also proposed to be vigilant for a potentially fatal arrhythmia, tip-twisting ventricular tachycardia (TdP). They suggested that QT interval prolongation is usually caused by drugs with hERG-blocking

properties, this adverse reaction was also found in our data as well [31]. High intestinal fluid secretion and diarrhea may lead to increased fecal excretion of potassium ions (K^+), while loss of intestinal fluids may trigger a secondary elevation of aldosterone, which further promotes renal excretion of potassium, ultimately leading to hypokalemia.Potassium levels are essential for normal heart function, and both hyperkalemia and hypokalemia can lead to cardiac dysfunction [32].

Although the mechanism of action of lubiprostone is primarily limited to the intestinal tract, long-term use may also affect other systems. Examples include metabolic and nutritional disorders, reproductive and breast disorders, and neoplasms (benign, malignant, and unspecified). In the case of reproductive and breast disorders, for example, Rubiprost may indirectly affect the body's secretion of dopamine and 5-hydroxytryptophan (5-HT), which may suppress prolactin in breast tissue. Indirect effects of 5-hydroxytryptophan (e.g., 5-hydroxytryptophan 1 A, 5-hydroxytryptophan 2 A, 5-hydroxytryptophan 2B, etc.) on prolactin secretion have been reported [33]. John Cuppoletti et al.'s study demonstrates that lubiprostone suppresses human uterine smooth muscle activity via ClC-2 Cl^- channel activation, inducing membrane hyperpolarization and reducing intracellular Ca^{2+} without EP receptor involvement. In contrast, PGE_2/PGE_1 enhance contraction through EP_1/EP_3 receptor-mediated Ca^{2+} mobilization, depolarization, and cAMP elevation. These opposing mechanisms highlight lubiprostone's potential as a prostaglandin-independent therapeutic agent for uterine hypercontractility, offering a novel pathway distinct from conventional prostaglandin signaling [34]. Cerebral palsy is a group of non-progressive neurological disorders that emerge in infancy or early childhood and primarily affect movement and posture. In our study, only 24 cases under the age of 18 were included. Although cerebral palsy was identified as a positive signal across all four detection methods, this association may not necessarily reflect a true drug-related adverse event, but rather a potential artifact. Individuals with cerebral palsy often experience gastrointestinal dysmotility, altered drug absorption, and multiple comorbidities, which could contribute to a higher likelihood of adverse event reporting in spontaneous reporting systems. All of these factors may contribute to the development of adverse events, but further data on larger samples and in-depth mechanistic studies are needed for clarity.

Limitations

This real-world observational study has several limitations. First, FAERS is a spontaneous reporting system that relies on voluntarily submitted data, a characteristic that may lead to underreporting and incomplete data, which may affect the stability and reliability of adverse event data and lead to potential bias. Second, our analytic approach mainly detects the strength of safety signals and establishes statistical associations; however, it does not determine the causal relationship between risk or drug and adverse events. Therefore, further clinical studies are needed to confirm causality (e.g., WHO-UMC criteria or Naranjo scale). Notably, Japan (35.24%) and the United States (29.81%) were the countries with the highest reports of adverse reactions, implying potential geographical constraints in our dataset. Subsequent studies could benefit from more robust prospective investigations that integrate clinical trials and epidemiological studies to provide a more precise evaluation of the safety risks associated with lubiprostone. Some adverse events, despite having low case numbers, showed strong signal strength and may warrant further mechanistic investigation to determine potential underlying biological or pharmacological causes. Nonetheless, pharmacovigilance using FAERS facilitates access to real-world datasets and enables early detection of drug safety signals. This study provides valuable insights into the safe use of medications and informs subsequent clinical practice.

Conclusion

This study provides a robust scientific foundation for evaluating the safety of lubiprostone through comprehensive and detailed analysis, offering essential data to support medical decision-making and public health policies. The study identified rare but important systemic adverse reactions, as well as specific adverse reactions not previously documented. Of particular concern was ischemic colitis, a serious gastrointestinal disorder that requires special clinical attention. Despite data limitations, these findings serve as valuable reference points for future in-depth research and regulatory initiatives. The study also delved into the potential mechanisms behind the rare systemic adverse reactions to lubiprostone, offering a thorough understanding of the molecular processes involved.

Abbreviations

FAERS	FDA Adverse Event Reporting System
ROR	Ratio of ratios
PRR	Proportional reporting ratio
BCPNN	Bayesian Confidence Propagation Neural Network
MGPS	Multi-Item Gamma Poisson Shrinker
SOCs	System Organ Classes
PTs	preferred terms
CIC	Chronic idiopathic constipation
IBS	Irritable bowel syndrome
AEs	Adverse drug events
IC	Ischemic colitis
TdP	Twisting ventricular tachycardia

Acknowledgements

This study was performed using open-source data provided by the FAERS database, and we thank all those who provided information for this database.

Author contributions
Y-W and Q-L conceived the study. CL-Y edited the paper conducted the data analysis, Q-L wrote all sections of paper. Q-L, JJ-Z, Y-W, XS-D, and CL-Y edited the manuscript.

Funding
The study was funded by the Shanxi Province "136" Revitalization Medical Project Construction Fund, and the Key R&D Program of Shanxi Province (202102130501015) provided financial support, and Research and Innovation Team Project for Scientific Breakthroughs at Shanxi Bethune Hospital (2024ZHANCHI06).

Data availability
Publicly available datasets were analyzed in this study. This data can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Declarations

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacy, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China
[2]Department of General Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China
[3]Department of Pharmacy, First Hospital of Shanxi Medical University, Taiyuan, China

Received: 15 November 2024 / Accepted: 12 May 2025
Published online: 22 May 2025

References

1. Vazquez Roque M, Bouras EP. Epidemiology and management of chronic constipation in elderly patients. Clin Interv Aging. 2015;10:919–30.
2. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and Meta-analysis. Am J Gastroenterol. 2011;106(9):1582–92.
3. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet. 2020;396(10263):1675–88.
4. Drossman DA, Hasler WL. Rome IV-Functional GI disorders: disorders of Gut-Brain interaction. Gastroenterology. 2016;150(6):1257–61.
5. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. Nat Rev Gastroenterol Hepatol. 2020;17(8):473–86.
6. Chang L, Chey WD, Imdad A, Almario CV, Bharucha AE, Diem S, Greer KB, Hanson B, Harris LA, Ko C, et al. American gastroenterological Association-American college of gastroenterology clinical practice guideline: Pharmacological management of chronic idiopathic constipation. Gastroenterology. 2023;164(7):1086–106.
7. Li F, Fu T, Tong WD, Liu BH, Li CX, Gao Y, Wu JS, Wang XF, Zhang AP. Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2016;91(4):456–468.
8. 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(2):294–301.
9. 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(1):170–7.
10. Sugimoto M, Murata M, Mizuno H. Differences in efficacy and safety of Lubiprostone used for idiopathic vs opioid-induced constipation: meta-analysis of East Asian and Western populations. J Clin Biochem Nutr. 2020;66(3):184–92.
11. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519–23.
12. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–6.
13. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315–21.
14. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10(7):796–803.
15. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9):1582–91.
16. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of Lubiprostone in patients with chronic constipation. Dig Dis Sci. 2010;55(4):1090–7.
17. Chey WD, Drossman DA, Johanson JF, Scott C, Panas RM, Ueno R. Safety and patient outcomes with Lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2012;35(5):587–99.
18. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of Lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. Dig Dis Sci. 2011;56(9):2639–45.
19. Sherid M, Sifuentes H, Samo S, Deepak P, Sridhar S. Lubiprostone induced ischemic colitis. World J Gastroenterol. 2013;19(2):299–303.
20. Lunsford TN, Harris LA. Lubiprostone: evaluation of the newest medication for the treatment of adult women with constipation-predominant irritable bowel syndrome. Int J Womens Health. 2010;2:361–74.
21. Bassil AK, Borman RA, Jarvie EM, McArthur-Wilson RJ, Thangiah R, Sung EZ, Lee K, Sanger GJ. Activation of prostaglandin EP receptors by Lubiprostone in rat and human stomach and colon. Br J Pharmacol. 2008;154(1):126–35.
22. Suh DC, Kahler KH, Choi IS, Shin H, Kralstein J, Shetzline M. Patients with irritable bowel syndrome or constipation have an increased risk for ischaemic colitis. Aliment Pharmacol Ther. 2007;25(6):681–92.
23. Song J, Yin J, Xu X, Chen J. Prokinetic effects of large-dose Lubiprostone on Gastrointestinal transit in dogs and its mechanisms. Am J Transl Res. 2015;7(3):513–21.
24. Spicknall KE, Zirwas MJ, English JC 3. Clubbing: an update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance. J Am Acad Dermatol. 2005;52(6):1020–8.
25. Uppal S, Diggle CP, Carr IM, Fishwick CW, Ahmed M, Ibrahim GH, Helliwell PS, Latos-Bielenska A, Phillips SE, Markham AF, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet. 2008;40(6):789–93.
26. Kawamoto R, Kikuchi A, Ninomiya D, Kumagi T. Clubbed digits presumably caused by Lubiprostone. Intern Med. 2021;60(15):2499–502.
27. Mizumori M, Akiba Y, Kaunitz JD. Lubiprostone stimulates duodenal bicarbonate secretion in rats. Dig Dis Sci. 2009;54(10):2063–9.
28. De Lisle RC, Mueller R, Roach E. Lubiprostone ameliorates the cystic fibrosis mouse intestinal phenotype. BMC Gastroenterol. 2010;10:107.
29. Sumida K, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, Yamagata K, Kalantar-Zadeh K, Kovesdy CP. Constipation and risk of death and cardiovascular events. Atherosclerosis. 2019;281:114–20.
30. Zhang W, Wang H, Yang S, Pang X, Hu W, Zhang G, Xin X. Post-marketing safety assessment of constipation drugs: a real-world pharmacovigilance study based on FAERS database. Expert Opin Drug Saf. 2025;18:1–12.
31. Raschi E, De Ponti F. Lubiprostone: Pharmacokinetic, pharmacodynamic, safety and regulatory aspects in the treatment of constipation-predominant irritable bowel syndrome. Expert Opin Drug Metab Toxicol. 2014;10(2):293–305.
32. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J. 2017;38(38):2890–6.
33. Chien HY, Chen SM, Li WC. Dopamine receptor agonists mechanism of actions on glucose Lowering and their connections with prolactin actions. Front Clin Diabetes Healthc. 2023;4:935872.

34. Cuppoletti J, Malinowska DH, Chakrabarti J, Ueno R. Effects of Lubiprostone on human uterine smooth muscle cells. Prostaglandins Other Lipid Mediat. 2008;86(1–4):56–60.

Publisher's note