Heliyon 10 (2024) e34837

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Pharmacovigilance analysis of orlistat adverse events based on the FDA adverse event reporting system (FAERS) database

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ARTICLE INFO

Keywords:
Orlistat
Adverse events
FAERS
Pharmacovigilance

ABSTRACT

Objective: Based on the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database, we analyzed the signals of potential adverse events (AEs) of orlistat in the real world to provide a reference for its safe clinical use.
Methods: The FAERS database and OpenVigil 2.1 were used to obtain data on adverse events of orlistat from the first quarter of 2004 to the first quarter of 2023, and to analyze the population in which the adverse events occurred. And the signals of their potential adverse events were mined using reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN) and empirical Bayesian geometric mean (EBGM).
Result: A total of 21,079 reports of adverse events with orlistat as the primary suspected drug were collected in this study. Using four disproportionate analyses, we screened 117 preferred terms (PTs) involving 18 system organ classes (SOCs). We found that the most common adverse events at SOC level for orlistat remained "gastrointestinal disorders", while "metabolism and nutrition disorders", "renal and urinary disorders", "musculoskeletal and connective tissue disorders" and "hepatobiliary disorders" also ranked high in the number of case reports. In addition, at the PT level, we identified several new signals of adverse events not mentioned in the specification, including "lipiduria", "anal haemorrhage", "rectal haemorrhage", "haematochezia", "sigmoiditis", "diverticulitis" and "muscle spasms".
Conclusion: Most of the adverse events found in this study are consistent with the results described in the drug label. At the same time, we also found some new adverse events, which require more prospective studies to verify and elucidate their relationship with orlistat.

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https://doi.org/10.1016/j.heliyon.2024.e34837
Received 6 April 2024; Received in revised form 13 July 2024; Accepted 17 July 2024
Available online 18 July 2024

1. Introduction

Orlistat is a weight-loss drug that does not act on the central nervous system and reduces the metabolism and absorption of dietary fat by inhibiting gastric lipase and pancreatic lipase activity [1]. Recent studies have shown that orlistat further affects body mass and visceral adiposity by regulating adipokines [2], gut hormones [3] and gut microbes [4,5]. Meanwhile, several studies have demonstrated the efficacy of orlistat for weight control in obese patients with concomitant type 2 diabetes mellitus [6], cardiovascular disease [7], and patients with polycystic ovary syndrome [8], as well as in antitumor therapy [9,10].

With the extensive revelation of the potential therapeutic effects of orlistat, its safety concerns are increasingly being closely monitored and emphasized. Studies have shown that the most common adverse events (AEs) to orlistat are mainly gastrointestinal tract, and it is known that about 8 % of patients drop out of clinical trials due to gastrointestinal AEs [11]. In addition, orlistat may cause serious AEs such as oxalate crystallization-related acute kidney injury [12], cutaneous leukocyte-crushing vasculitis [13], and even death from liver failure in patients taking orlistat [14]. Due to the lethality of some liver injuries, the US Food and Drug Administration (FDA) also listed liver injury as an AEs with a black box warning for orlistat in 2010. In addition to this, in recent years, some surprising related case reports have occurred, such as orlistat can lead to HIV rebound by reducing the absorption of antiretroviral drugs [15]. Currently, most of the AEs warning information involving orlistat is based on observational studies and case reports, and there is a lack of large-scale real-world safety re-evaluation of orlistat. Therefore, there is a need to dig deeper into the AEs occurring with orlistat in clinical practice to reduce its potential medication risk.

The FDA Adverse Event Reporting System (FAERS) is the largest public database of AEs of drugs in the world, which collects thousands of spontaneous reports of adverse drug events in the real world, and can reflect to some extent the occurrence of real-world drug AEs [16]. The disproportionality analysis (DA), a method commonly used in pharmacovigilance studies, has demonstrated its irreplaceable importance in identifying rare and unpredictable AEs [17,18]. Based on the FAERS database, researchers have already utilized DA to mine potential signals of adverse drug events for pharmacovigilance, which provides a reference for clinical medication use and reduces the risk of patient medication [19–21]. In this study, four DAs were utilized for signal mining and risk analysis of orlistat-related adverse events data in the FAERS database to provide a reference for the subsequent safe use of orlistat.

2. Method

2.1. Data sources and cleaning

FAERS is a database used for post-marketing monitoring of all drugs and therapeutic biological products approved by FDA. Its quarterly data contains seven information sets, including drug-related details (DRUG), patient outcomes (OUTC), demographic and administrative information (DEMO), indications for use or diagnosis (INDI), reports on adverse drug reactions (REAC), sources of report (RPSR), and drug therapy duration (THER) [22,23]. OpenVigil 2.1 is a publicly available tool for extracting FAERS-related data [24]. In this study, OpenVigil 2.1 was used to obtain AEs data in FAERS from the first quarter of 2004 to the first quarter of 2023, and drug names were standardized according to Drugbank and Drugs@FDA. For the collected data, first, we selected only the reports with orlistat as the primary suspected drug and excluded the remaining reports. Second, in adherence to the guidelines of FDA, our study implemented a rigorous process to identify and eliminate duplicate reports. We selected the most recent FDA_DT items with the same CASEID. In cases where CASEID and FDA_DT are the same, we prioritized the higher PRIMARYID. Finally, we conducted pharmacovigilance studies using AEs data from clean and standardized case reports. In this process, AEs were standardized for mapping analysis according to the preferred term (PT) and system organ class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA 25.0) terminology, and we used R Studio to quickly complete the matching step. In addition, we performed a descriptive analysis of the demographic and clinical characteristics of orlistat-related case reports, such as patient gender, age, and outcomes of serious AEs.

2.2. Methods of data analysis

The classic fourfold table was used in this study (Table 1) [25]. Signal mining of orlistat AEs was performed by reporting odds ratio (ROR) [26,27], proportional reporting ratio (PRR) [28], Bayesian confidence propagation neural network (BCPNN) [29] and empirical Bayesian geometric mean (EBGM) [30]. The ROR and PRR methods were used to assess the association between drugs and AEs mainly by calculating ROR values, PRR values and 95 % confidence limits by frequency counting method. Larger ROR and PRR values indicate a stronger signal and a greater correlation between the target drug and AEs. In the BCPNN method, the strength of dependence between a drug and an AE is calculated using a logarithmic nonproportionality measure known as the information component (IC). The 95 % lower confidence limit indicates a statistically significant disproportionality between the expected and reported rates of the drug and

Table 1
Fourfold table of disproportionality analyses.

Medicine	Target adverse events reported	Other adverse events reported	Summation
Target drugs	**a**	**b**	**a+b**
Other drugs	**c**	**d**	**c + d**
Summation	**a+c**	**b + d**	**a+b + c + d**

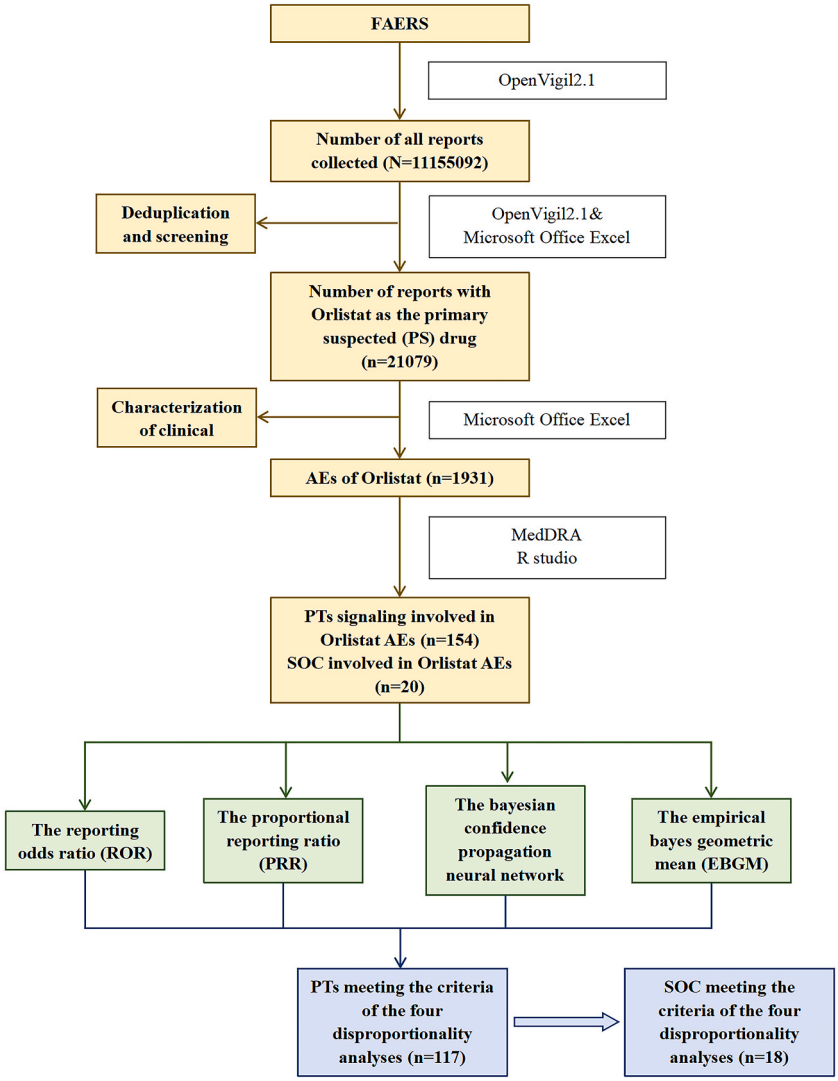

Fig. 1. This flowchart shows the details of how we screened orlistat for adverse events from the FAERS database.

the AE. High IC values and 95 % lower confidence limits indicate a strong correlation between the drug and AEs [18]. This method requires relatively low data quality, yet detects strong statistical correlations. The EBGM method, although less sensitive, allows for stratified analysis for population factors. Compared to the ROR and PRR methods, the Bayesian method has the advantages of high specificity, stable signal, and low probability of misclassification, which makes it a more prudent method [31]. Therefore, during the DA of PTs, we will focus more on the magnitude of the IC025 value. The detailed process of data analysis in this study is demonstrated in the flowchart (Fig. 1), the formulas of the four DAs methods and their standard conditions are as follows :

(i) ROR method

$$\mathrm{ROR} = \frac{ad}{bc}$$

$$95\%\ \mathrm{CI} = e^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The criteria of positive safety signal detection: the lower limit of 95 % CI > 1, N ≥ 3.

(ii) PRR method

$$PRR = \frac{a(c+d)}{c(a+b)}$$

$$\chi^2 = \frac{(a+b+c+d)(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)}$$

The criteria of positive safety signal detection: PRR $\geq$2, $\chi^2 \geq 4$, N $\geq$ 3.

(iii) BPCNN method

$$IC = \log_2 \frac{a(a+b+c+d)}{(a+c)(a+b)}$$

$$95\%\ CI = E(IC) \pm 2 \times \sqrt{V(IC)}$$

The criteria of positive safety signal detection: IC025 > 0 (IC025: the lower bound of 95 % CI).

(iv) EBGM method

$$EBGM = \frac{a(a+b+c+d)}{(a+c)/(a+b)}$$

$$95\%\ CI = e^{\ln(EBGM) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The criteria of positive safety signal detection: EBGM05 > 2 (EBGM05: the lower bound of 95 % CI).

In our study, meaningful signals of AEs should simultaneously meet the screening criteria of four DAs. The signals of screened AEs were referred to orlistat related literature [11,32,33] and drug labels in the Drug Approvals and Databases (https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases). If the screened meaningful signals of AEs were not within the drug label then they were new AEs signals for orlistat.

Table 2
Clinical characteristics of case reports with orlistat from the Food and Drug Administration Adverse Event Reporting System database **(2004 Q1– 2023 Q1)**.

Characteristics	Case Number	Case Proportion
Number of events	21079	
Gender		
Male	1580	7.50 %
Female	12959	61.48 %
Unknown	6540	31.03 %
Age		
<19	157	0.74 %
20–29	1274	6.04 %
30–39	2041	9.68 %
40–49	2351	11.15 %
50–59	2176	10.32 %
60–69	1195	5.67 %
70–79	432	2.05 %
>80	71	0.34 %
Unknown	11382	54.00 %
Serious Outcome		
Hospitalization	1100	5.22 %
Disability	135	0.64 %
Life-threatening	111	0.53 %
Death	107	0.51 %
Unknown	19626	93.11 %
Reported Countries		
US	18945	89.88 %
GB	1005	4.77 %
DE	80	0.38 %
BR	65	0.31 %
FR	63	0.30 %
Others	921	4.37 %

3. Result

3.1. General analysis of AEs for orlistat

A total of 11,155,092 reports of AEs were obtained in this study, and 21079 (0.18 %) of AEs were reported with orlistat as the primary suspect drug. In terms of reporting gender, 12,959 cases were reported by females and 1580 cases were reported by males. The top three reporting age groups were 40–49 (11.15 %), 50–59 (10.32 %) and 30–39 (9.68 %). The country with the highest number of reported sources was the United States (89.88 %), followed by the United Kingdom (4.77 %). Among the reported outcomes, hospitalization (5.22 %) was the most common serious outcome. In addition to this, 111 cases of life threatening (0.53 %) and 107 cases of death (0.51 %) were reported (Table 2).

3.2. Analysis of AEs based on SOC levels

The AEs for orlistat involved a total of 20 SOCs, of which 18 SOCs met the criteria of four DAs (Table 3). Among all SOCs, gastrointestinal disorders (n = 16247) topped the list of case reports. In addition, the top 10 SOCs included general disorders and administration site conditions (n = 5422), investigations (n = 1857), product issues (n = 1327), metabolism and nutrition disorders (n = 854), renal and urinary disorders (n = 515), musculoskeletal and connective tissue disorders (n = 376), hepatobiliary disorders (n = 351), nervous system disorders (n = 333), reproductive system and breast disorders (n = 227).

3.3. Analysis of AEs based on PT levels

The AEs for orlistat involved 154 PTs signals and 117 PTs signals that also met the four DAs, and SOCs were also classified for these 117 PTs (Supplementary table). In order to more accurately assess AEs directly related to the taking of orlistat, AEs that may be related to drug characteristics, the process of obesity itself, or other nonpharmacologic factors were ignored in this study (e.g. "general

Table 3
Orlistat adverse events were ranked in descending order by case reports at the system organ class (SOC) level in the Food and Drug Administration Adverse Event Reporting System (FAERS).

SOC	SOC Code	Cases Reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
Gastrointestinal disorders	10017947	16247	42.72 (41.37–44.12)	10.56 (10.48–10.64)	148969.36	3.38 (3.31)	10.38 (10.05)
General disorders and administration site conditions	10018065	5422	4.42 (4.28–4.56)	3.54 (3.46–3.62)	10581.06	1.82 (1.72)	3.52 (3.42)
Investigations	10022891	1857	7.7 (7.34–8.08)	7.11 (6.81–7.43)	9741.51	2.81 (2.65)	7.03 (6.7)
Product issues	10077536	1327	7 (6.62–7.4)	6.62 (6.28–6.98)	6304.70	2.71 (2.52)	6.55 (6.19)
Metabolism and nutrition disorders	10027433	854	10.9 (10.17–11.68)	10.5 (9.82–11.22)	7214.91	3.37 (3.13)	10.31 (9.62)
Renal and urinary disorders	10038359	515	4.25 (3.89–4.64)	4.17 (3.83–4.54)	1237.26	2.05 (1.76)	4.14 (3.79)
Musculoskeletal and connective tissue disorders	10028395	376	2.34 (2.11–2.59)	2.31 (2.09–2.56)	280.73	1.21 (0.86)	2.31 (2.08)
Hepatobiliary disorders	10019805	351	3.42 (3.08–3.8)	3.38 (3.05–3.75)	587.17	1.75 (1.4)	3.37 (3.03)
Nervous system disorders	10029205	333	31.85 (28.49–35.6)	31.36 (28.1–35)	9237.02	4.89 (4.52)	29.66 (26.53)
Reproductive system and breast disorders	10038604	227	4.26 (3.74–4.86)	4.23 (3.71–4.82)	556.66	2.07 (1.63)	4.2 (3.69)
Injury, poisoning and procedural complications	10022117	206	4.8 (4.18–5.51)	4.76 (4.16–5.46)	607.67	2.24 (1.78)	4.73 (4.12)
Endocrine disorders	10014698	147	3.59 (3.05–4.23)	3.58 (3.04–4.2)	271.30	1.83 (1.29)	3.56 (3.02)
Psychiatric disorders	10037175	119	11.78 (9.82–14.13)	11.72 (9.78–14.05)	1141.28	3.52 (2.92)	11.49 (9.57)
Surgical and medical procedures	10042613	90	3.98 (3.24–4.9)	3.97 (3.23–4.88)	198.56	1.98 (1.3)	3.95 (3.21)
Infections and infestations	10021881	49	3.11 (2.35–4.12)	3.11 (2.35–4.11)	69.51	1.63 (0.71)	3.09 (2.34)
Skin and subcutaneous tissue disorders	10040785	46	5.7 (4.26–7.63)	5.69 (4.26–7.61)	176.00	2.5 (1.55)	5.64 (4.22)
Respiratory, thoracic and mediastinal disorders	10038738	40	4.24 (3.11–5.79)	4.24 (3.1–5.78)	98.06	2.07 (1.07)	4.21 (3.08)
Vascular disorders	10047065	4	20.52 (7.56–55.71)	20.51 (7.56–55.69)	71.47	4.31 (1.58)	19.78 (7.29)

Abbreviations: SOC, system organ class; CI, confidence interval; ROR, reporting odds ratio; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

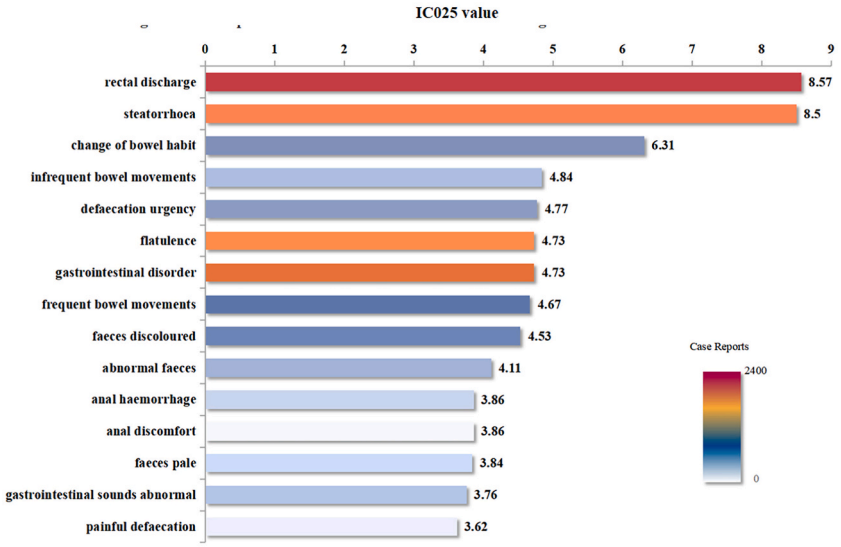

Fig. 2. Signals of the top 15 adverse events at the preferred term level with IC025 values in gastrointestinal disorders.

disorders and administration site conditions" and "product issues", etc.). In addition, we focused on the PTs associated with the SOCs that ranked among the top 10 in terms of the number of case reports, especially the AEs that were directly related to the organs of the visceral system. In the gastrointestinal disorders, there were signals of up to 42 AEs at the PT level, and the top three PTs with IC025 values were rectal discharge (n = 2217, ROR = 2687.09, PRR = 2404.58, IC025 = 8.57, EBGM05 = 392.95), steatorrhea (n = 1451, ROR = 2406.6, PRR = 2241.01, IC025 = 8.5, EBGM05 = 380.35), and change of bowel habit (n = 222, ROR = 142.26, PRR = 140.77, IC025 = 6.31, EBGM05 = 95.98) (Fig. 2). In the renal and urinary disorders, the top three PTs with IC025 values were lipiduria (n = 59, ROR = 15625.75, PRR = 15582.02, IC025 = 7.8, EBGM05 = 125.05), hyperoxaluria (n = 8, ROR = 62.16, PRR = 62.14, IC025 = 3.61, EBGM05 = 26.77), oxalosis (n = 3, ROR = 42.83, PRR = 42.83, IC025 = 2.21, EBGM05 = 12.24). In the hepatobiliary disorders, the top three PTs with IC025 values were cholelithiasis (n = 118, ROR = 4.18, PRR = 4.16, IC025 = 1.45, EBGM05 = 3.45), gallbladder pain (n = 8, ROR = 10.7, PRR = 10.7, IC025 = 1.32, EBGM05 = 5.22), gallbladder disorder (n = 83, ROR = 4.13, PRR = 4.12, IC025 = 1.32, EBGM05 = 3.3). In the reproductive system and breast disorders, the top three PTs with IC025 values were menstrual disorder (n = 96, ROR = 12.72, PRR = 12.67, IC025 = 2.96, EBGM05 = 10.12), polymenorrhoea (n = 22, ROR = 8.1, PRR = 8.09, IC025 = 1.66, EBGM05 = 5.24) and vaginal pain (n = 4, ROR = 11.24, PRR = 11.24, IC025 = 0.77, EBGM05 = 4.09) (Fig. 3).

Notably, we also identified signals of AEs for orlistat not recorded in the label and the relevant literature, including lipiduria (n = 59, ROR = 15625.75, PRR = 15582.02, IC025 = 7.8, EBGM05 = 125.05), anal haemorrhage (n = 57, ROR = 27.95, PRR = 27.88, IC025 = 3.86, EBGM05 = 20.32), rectal haemorrhage (n = 302, ROR = 8.45, PRR = 8.34, IC025 = 2.66, EBGM05 = 7.34), haematochezia (n = 251, ROR = 6.09, PRR = 6.03, IC025 = 2.16, EBGM05 = 5.27), sigmoiditis (n = 3, ROR = 20.06, PRR = 20.06, IC025

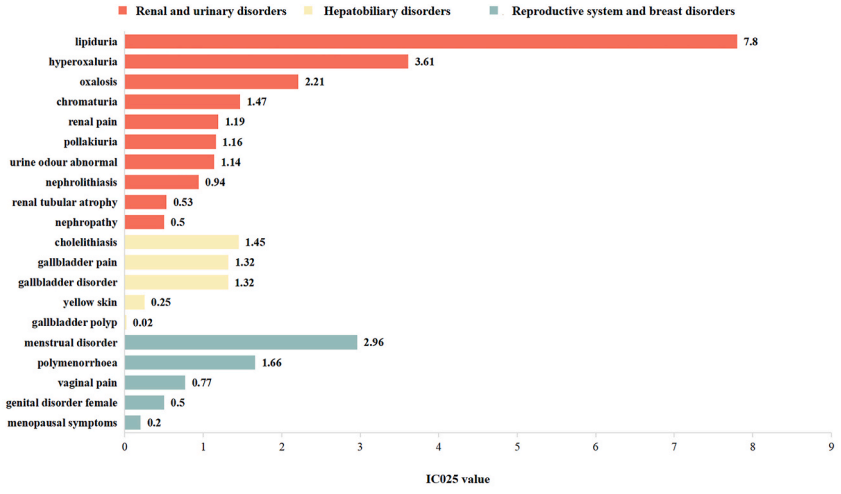

Fig. 3. The PTs in SOCs related to "renal and urinary disorders", "hepatobiliary disorders" and "reproductive system and breast disorders" are listed in descending order of IC025 value.

Table 4
The top seven new adverse events of orlistat at the preferred term (PT) level ranked in descending order by IC025 value in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

PT	SOC	Case Reports	ROR(95 % CI)	PRR(95 % CI)	χ2	IC(IC025)	EBGM(EBGM05)
lipiduria	Renal and urinary disorders	59	15625.75 (3817.64–63956.89)	15582.02 (3807.45–63769.61)	30138.56	9 (7.8)	511.85 (125.05)
anal haemorrhage	Gastrointestinal disorders	57	27.95 (21.41–36.49)	27.88 (21.37–36.37)	1403.15	4.73 (3.86)	26.53 (20.32)
rectal haemorrhage	Gastrointestinal disorders	302	8.45 (7.53–9.47)	8.34 (7.45–9.34)	1923.77	3.04 (2.66)	8.23 (7.34)
haematochezia	Gastrointestinal disorders	251	6.09 (5.37–6.9)	6.03 (5.32–6.82)	1042.21	2.58 (2.16)	5.97 (5.27)
sigmoiditis	Gastrointestinal disorders	3	20.06 (6.33–63.55)	20.06 (6.33–63.53)	52.34	4.28 (1.27)	19.36 (6.11)
diverticulitis	Gastrointestinal disorders	79	3.61 (2.9–4.51)	3.6 (2.89–4.49)	147.81	1.84 (1.11)	3.59 (2.87)
muscle spasms	Musculoskeletal and connective tissue disorders	373	2.32 (2.1–2.57)	2.3 (2.08–2.54)	274.69	1.2 (0.85)	2.29 (2.07)

Abbreviations: SOC, system organ class; PT, preferred term; CI, confidence interval; ROR, reporting odds ratio; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

= 1.27, EBGM05 = 6.11), diverticulitis (n = 79, ROR = 3.61, PRR = 3.6, IC025 = 1.11, EBGM05 = 2.87) and muscle spasms (n = 373, ROR = 2.32, PRR = 2.3, IC025 = 0.85, EBGM05 = 2.07) (Table 4).

4. Discussion

As one of the few over-the-counter weight loss medications, orlistat is easy and convenient to obtain, which means that the drug can easily be used without the guidance and supervision of a doctor. In our collection of reports of orlistat AEs, the number of case reports from orlistat over-the-counter (n = 16,350) was much greater than the number of case reports from prescription drugs (n = 1231). In this context, it is of paramount importance to raise public awareness and alertness to the safety of their medication. This study utilized the FAERS database for DAs of orlistat AEs reports. We have not only focused on its occurrence characteristics in the general population, especially important AEs related to the gastrointestinal tract, liver, gallbladder and kidneys, but also identified AEs not mentioned in the drug label. These findings are discussed in detail below, with the aim of providing healthcare professionals and patients with more comprehensive information on the safe use of the drug.

4.1. Population analysis of AEs

A total of 21,079 reports of AEs with orlistat as the main primary suspect drug were retrieved in this study. At the age level, the majority of patients who experienced AEs with orlistat were concentrated in the age range of 30–59 years, with the number of cases amounting to 6,568, or 67.73 % of the known age reports, while the incidence of obesity is known to be concentrated in this range in terms of age as well [34]. At the gender level, excluding reports of unknown gender, the number of cases of AEs with orlistat was about 8.20 times higher in women than in men; however, there is a lack of studies that systematically analyze the gender differences in AEs with orlistat. Since orlistat is primarily used for weight management, we initially hypothesized that this gender difference might be related to differences in obesity rates between men and women. However, according to recent statistics, although the rate of obesity is higher in women than in men, there is not more than a twofold difference [35], and thus the difference in the rate of obesity between the two genders may not be the reason for such a significant difference in the number of cases. However, it is worth noting that obese women are more likely to experience symptoms of depression, anxiety and stress, and women are also more conscious of weight control than men [36,37]. These factors may have contributed to the relatively large proportion of the female population taking orlistat. Therefore, whether there are gender differences in the occurrence of AEs of orlistat and the underlying reasons behind them still need to be further researched and investigated.

4.2. Analysis of known AEs to orlistat

The most common and significant signal of AEs at the SOC level was gastrointestinal disorders, where the top 3 PTs with IC025 values were rectal discharge, steatorrhea and change of bowel habit. This finding is consistent with the most common AEs listed in the drug label of orlistat, and this consistency partly confirms the reliability of our data analysis methodology. Side effects related to fat malabsorption, including oily fecal spotting, abdominal pain, flatulence with discharge, and fatty/oily feces, are known to occur in more than 20 % of patients treated with orlistat, most often within 3 months of dosing, and the incidence of which increases with the amount of fat in the food consumed [38,39]. And a case report stated that concomitant administration of orlistat and an olestra-containing snack food may exacerbate AEs in the gastrointestinal tract [40]. It has also been claimed that the incidence of such AEs may be reduced by the addition of natural fiber (psyllium mucilloid) [41]. Therefore, it is necessary to be aware of this potential drug-food interaction in patients receiving orlistat for the treatment of obesity. In addition to this, "pancreatic enzymes increased (n = 8, ROR = 6.33, PRR = 6.33, IC025 = 0.58, EBGM05 = 3.12)" were also in our results. Several case reports have shown that after taking orlistat, patients experienced varying degrees of abdominal pain and some had increased pancreatic enzymes, which were later diagnosed as drug-related pancreatitis secondary to orlistat [42–44]. In our outcome screening, oedematous pancreatitis (n = 3, ROR = 6.58, PRR = 6.58, IC025 = −0.24, EBGM05 = 2.08) had positive signals at the ROR and PRR levels despite not satisfying all the criteria of four DAs. There are no studies on the mechanism of orlistat-induced pancreatitis, but given that higher BMI levels significantly increase the risk of acute pancreatitis and the high lethality of pancreatitis [45], it is important to be vigilant about the possibility of pancreatitis if abdominal pain and "pancreatic enzymes increased" occur in obese patients taking orlistat.

Besides gastrointestinal diseases, we also found that orlistat can cause AEs in the kidneys, liver, gallbladder and reproductive systems. Although their number of case reports is not as high as that of the gastrointestinal system, some of the AEs associated with them, when they occur, cause serious consequences. For the renal and urinary disorders, it is now widely recognized that renal injury is associated with orlistat-induced intestinal hyperoxaluria [46] and oxalate nephropathy [47]. In the label, renal injury is only mentioned as a rare AE that you should be aware of when taking orlistat. However, orlistat-induced kidney damage, such as renal tubular atrophy and interstitial fibrosis, is usually asymptomatic and its progression is insidious. Discontinuing orlistat only stops the progression of the disease but does not reverse the renal impairment that has already occurred [47,48]. Some tests, such as urinalysis and ultrasonography, may be difficult to detect, and renal biopsies may be interfered with overlooked by the patient's obesity itself or renal insufficiency. Meanwhile, several cases have shown that there is no clear relationship between the time of onset of renal injury and the duration of orlistat treatment [49]. Several studies have been conducted to analyze the time to onset (TTO) of a particular AE occurring with the drug using raw data from FARES [50,51]. Limited by our data processing methods, although TTO analysis of orlistat-induced renal injury was not performed in our study, it is undeniable that it is extremely important to closely monitor renal function in patients while taking orlistat. Whereas the effects of orlistat on the hepatic diseases are currently controversial. On the one

hand, clinical cases of severe liver injury due to orlistat have become common in recent years [52]. In known cases, patients usually develop liver injury and elevated hepatic enzymes after taking orlistat for 2–12 weeks, and patients with severe liver injury may develop liver failure, even progressing to death or requiring liver transplantation [53,54]. It is currently thought that hepatic injury is associated with orlistat-induced hypersensitivity reactions, but this has not been confirmed [53]. On the other hand, recent studies have found that orlistat has therapeutic effects on non-alcoholic fatty liver disease (NAFLD) by lowering alanine aminotransferase, aspartate aminotransferase, triglycerides, and cholesterol [55,56]. Especially in NAFLD-associated hepatocellular carcinoma, orlistat may promote the treatment of hepatocellular carcinoma by regulating phosphatase and tensin homolog [57]. It is therefore necessary to explore the mechanism of action of orlistat on the liver in order to more fully assess its risks and benefits. For gallbladder diseases, according to relevant studies, orlistat may inhibit the release of cholecystokinin and affect gallbladder emptying [58]. Obese patients are themselves at high risk for gallbladder disease, so the occurrence of gallbladder-related diseases should be a concern when taking orlistat. For the reproductive system, this study also unearthed multiple signals of AEs associated with menstrual disorders in women, which is consistent with the fact that menstrual disorders are occasionally seen after taking orlistat as labeled in the insert. However, in patients with polycystic ovary syndrome, orlistat may have an improving effect on menstrual disorders [59].

4.3. Analysis of new AEs to orlistat

Our study also found AEs outside of the orlistat label and these new AEs included lipiduria, anal haemorrhage, rectal haemorrhage, haematochezia, sigmoiditis, diverticulitis and muscle spasms. There have been no direct studies in the literature on orlistat causing these new AEs, especially lipiduria. After reviewing a number of studies, we have hypothesized about the occurrence of new AEs with a view to providing new ideas for the study of AEs with orlistat.

Diverticulosis and diverticulitis, especially sigmoid diverticulitis, are the most common noncancerous lesions of the colon, and the specific pathogenesis of diverticulitis remains unidentified [60,61]. However, in patients with diverticulosis, observations have shown that inflammation at the diverticular opening is characterized by chronic inflammation with epithelial cell regeneration, macrophage-dominated immune response, enhanced cell adhesion, and abnormal cytokine expression [62]. Whereas studies have shown that orlistat treatment also causes alterations in secondary gut metabolites in mice on a low-fat diet, which affect the redox state of the colon and may lead to inflammation, oxidation, and mitochondrial dysfunction at the cellular level, which in turn increases the enhancement of the inflammatory response in the gut [63]. In addition, the differentiation between diverticulitis of the sigmoid colon and colon cancer can be very difficult [64]. Moreover, several studies have shown that the incidence of colon cancer is higher in patients with acute and complicated left colonic diverticulitis or sigmoid diverticulitis than in the general population [65–67]. Furthermore, studies have shown that orlistat not only causes histologic damage to the brush border membrane and connective tissue of the small intestinal mucosal villi, but also significantly increases the incidence of abnormal crypt foci in the colon, thereby increasing the risk of colon cancer [32,33]. Although an increased risk of colorectal cancer with orlistat was not observed in a large cohort analysis, the possibility that long-term use of orlistat may contribute to the risk of colorectal cancer cannot be ruled out due to the short follow-up period [68]. The American College of Physicians recommends that patients with acute and complicated left colonic diverticulitis undergo colonoscopy to rule out colorectal cancer [69]. In light of these findings, the presence of left-sided colonic diverticulitis after taking orlistat should be a cause for concern, and the association between diverticulitis, orlistat treatment, and colon cancer should be further investigated.

For gastrointestinal haemorrhage events, most of the AEs we screened focused on lower gastrointestinal haemorrhage. Currently, the main drug classes known to be associated with pharmacologic lower gastrointestinal haemorrhage include nonsteroidal anti-inflammatory drugs, antithrombotic drugs, as well as gastric acid inhibitors and proton pump inhibitors, whereas orlistat was not included [70–72]. However, orlistat has the property of affecting the absorption of fat-soluble vitamins [73], which includes malabsorption of vitamin E, an effect that may potentiate the anticoagulant effect of warfarin [74]. Because of the significant association between warfarin and acute lower gastrointestinal haemorrhage and diverticular haemorrhage [75], as well as the fact that obesity is considered an important risk factor for diverticulitis and diverticular haemorrhage [76,77], we cannot completely rule out the potential impact of orlistat on gastrointestinal haemorrhage in obese patients when it is used in combination with warfarin. Therefore, patients should also be aware of the effects of orlistat interactions with other medications while on the drug.

Muscle spasms are sudden, involuntary muscle contractions that are usually self-limiting, and muscle pain is one of the most common features of muscle spasms [78]. The physiopathologic mechanism by which orlistat causes muscle spasms is unknown, but for muscle pain, cases of myalgia with orlistat have been reported in both men and women [79,80]. It has been shown that myalgia may be associated with impaired cellular respiration due to coenzyme Q10 reduction by orlistat [80]. In addition, after 16 weeks of orlistat treatment, there was a significant decrease in serum 25-OH-D concentration [81], and vitamin D deficiency will lead to a decrease in muscle function [82], and even more so in hemifacial spasm and laryngospasm [83,84]. Therefore, further studies are essential to validate the relationship between orlistat and new AEs, which will contribute to a better understanding of the safety and rational use of the drug.

5. Limitations

First, the FAERS database, as a spontaneous reporting system, suffers from omissions and duplicate reports, as well as a lack of relevant background information on the occurrence of the AEs in question. This resulted in our inability to obtain the total number of orlistat users and the context of medication use, making it difficult to accurately predict the true incidence of AEs [85]. For example, 31.02 % of the reports in this study did not provide gender information and 54 % did not provide age information, which may affect the

objective reflection of the study results to the real world. Second, DAs by themselves cannot be used as a substitute for relative risk or ratio ratios. It typically shows only differences in reported frequencies. Although it can be used to detect signals of new or unusual AEs for drugs, it cannot indicate the actual risk of AEs [86]. In conclusion, although DAs and FAERS database are commonly used for pharmacovigilance signal detection, their results represent only statistical associations and still need to be validated by further studies such as clinical studies and epidemiology [87].

6. Conclusion

This study found that the most common AEs of orlistat remained concentrated in gastrointestinal disorders, further elucidating the potential effects of orlistat on the hepatobiliary, renal, as well as reproductive systems. Notably, we identified some new AEs, including lipiduria, anal haemorrhage, rectal haemorrhage, haematochezia, sigmoiditis, diverticulitis and muscle spasms, and these new signals of AEs were statistically highly correlated with orlistat. However, due to the limitations of the FAERS database and DAs, we have not yet been able to determine the causal relationship between orlistat and these new AEs, and future validation in combination with multifaceted comprehensive studies is still needed to provide more reliable and valid evidence for the rational clinical use of orlistat and the reduction of potential risks.

Ethics approval

Our study data were derived from publicly available adverse event reports from FAERS, and therefore this study did not require permission from the ethics committee to be conducted. At the same time, during the writing of this paper, we solemnly promise to strictly adhere to the principles outlined in the Declaration of Helsinki.

Funding

This study was funded by a grant from the Natural Science Foundation of Guangdong Province (Nos. 2021B1515140012, and 2023A1515010083), the Dongguan Science and Technology of Social Development Program (No. 20211800905342), the Medical Scientific Research Foundation of Guangdong Province (No. A2024398) ，the Research and Development Fund of Dongguan People's Hospital (No. k202005), the Guangdong Medical University Students' Innovation Experiment Program (Nos. 2021ZZDS006, 2022ZYDS003, 2022FYDB009, 2022FCDS003, 2023ZYDS001, 2023FZDS001, and 2023FYDB010), the Guangdong Medical University Students' Innovation and Entrepreneurship Training Program (Nos.GDMU2021003, GDMU2021049, GDMU2022031, GDMU2022047, GDMU2022063, GDMU2022077, GDMU2022078, GDMU2023008, GDMU2023015, GDMU2023026, GDMU2023042, and GDMU2023102), the Provincial and National College Students' Innovation and Entrepreneurship Training Program (Nos. 202210571008, S202210571075, 202310571031, S202310571047, S202310571078, S202310571063, and S202310571077), the Guangdong Medical University-Southern Medical University twinning research team project (No. 4SG24028G), the Cai Limin National Traditional Chinese Medicine Inheritance Studio and "Climbing 100″ Joint Merit Training Program Funded Project (No. PF100-2-01).

Data availability statement

Has data associated with your study been deposited into a publicly available repository?

Response: No. Our raw data were obtained from the FAERS database: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jinfeng Zhu: Writing – review & editing, Writing – original draft, Data curation. **Mianda Hu:** Writing – review & editing, Visualization, Data curation. **Yingshi Liang:** Validation, Formal analysis. **Mingjun Zhong:** Supervision, Methodology. **Zilin Chen:** Writing – original draft, Project administration. **Zhenjie Wang:** Writing – original draft, Software. **Yujia Yang:** Writing – original draft. **Ziyi Luo:** Writing – review & editing. **Wenqi Zeng:** Visualization, Investigation. **Jiahui Li:** Writing – original draft. **Yikuan Du:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation. **Yi Liu:** Writing – review & editing. **Chun Yang:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to sincerely thank Dr. Bin Zhao for his guidance and support of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34837.

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