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RESEARCH ARTICLE

Descriptive analysis of reported adverse events associated with anti-obesity medications using FDA Adverse Event Reporting System (FAERS) databases 2013–2020

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Abstract
Background Obesity is a globally growing health problem, and its treatment has been challenging. The use of anti-obesity medications (AOMs) has been associated with severe adverse events (AEs). Several AOMs have been withdrawn from the market owing to documented AEs. *Aim* To describe, estimate and characterize the frequency of AEs attributable to the use of the AOMs, and investigate previously unreported potential AEs associated with AOMs. *Method* Using the US FDA Adverse Event Reporting System (FAERS) between January 2013 and June 2020, a retrospective, descriptive analysis was conducted to analyze all major reported AEs and outcomes including death, life-threatening, hospitalization, disability, and required intervention or congenital anomaly. The total numbers of AEs reports, cases, adverse reactions and outcomes were calculated for each medication. *Results* A total of 18,675 unique AEs reports associated with AOMs used for 15,143 patients. The mean age was 49.8 years [SD 1.83], while most patients were female adults (73.4%). The most frequently reported AEs were nausea and vomiting, followed by dizziness and headache, drug ineffectiveness, cardiovascular diseases, and kidney complications. There were 21,229 unique outcomes, including 1039 deaths (fatality ratio of 4.9% of all analyzed reports), 1613 (7.6%) life-threatening events, 7426 (35%) hospitalizations, and 1249 (5.9%) disability cases. Phentermine/topiramate fatal cases represent 6% of the overall medication's reported AEs. Cardiovascular AEs represented 31%, 23%, and 22% of phentermine, liraglutide, and phentermine/topiramate total AEs, respectively. *Conclusion* The analysis of FAERS database revealed numerous serious AEs associated with AOMs. These AEs can lead to serious cardiovascular and kidney complications. It is necessary to continue and systematically monitor safety of AOMs' to optimize patient anti-obesity therapy.

Keywords Adverse events · Adverse reactions · Anti-obesity medications · Cardiovascular disease · Drug safety · Drug utilization · FDA Adverse Events Reporting System · Obesity

Impacts on practice

- Serious cardiovascular and kidney AEs seem to be attributed to the use of anti-obesity medications.
- Healthcare stakeholders should be aware of the AEs attributed to the use of the AOMs and their significant impact on patients' health.
- The utilization of AOMs should be closely monitored to avoid unnecessary AEs and all safety data collected in real life should be reported to pharmacovigilance systems.
- The proper use of the AOMs through following pharmacists' and physicians' instructions can help minimize their undesirable effects.

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Introduction

Obesity is defined as a body mass index (BMI) of ≥ 30 kg/m^2 and is caused by an imbalance between energy intake and expenditure. It affects nearly 100 million adults in the United States (US) in 2019, and it is universally identified as the fastest-growing public health challenge in the world [1–3]. Many studies have estimated the health burden of obesity and found that a wide range of health complications are correlated with obesity [4–8]. Patterson et al. [9] published a study in 2004 and found that BMI levels were significantly associated with medical conditions among women (37 of 41 conditions) and men (29 of 41 conditions). Additionally, A systematic review and meta-analysis study published in (2016) analyzed 230 cohort studies with 3.74 million deaths among more than 30 million participants to study the association between BMI and mortality risk. They found that overweight and obesity were significantly associated with an increase in the risk of all-cause mortality [10]. It is a global health crisis with detrimental impacts on the body systems, resulting in an exacerbated disease state.

Education and modifications to the obesogenic environment are effective long-term goals for preventing obesity; however, sustainable weight loss is difficult to achieve through lifestyle changes in the form of exercise or diet [11], and surgical or pharmacological treatment are required for those who are already obese. One thriving modality aimed at mitigating obesity and enhancing survival is bariatric surgeries. However, because of some concerns regarding surgical complications and perioperative mortality, guidelines recommend reserving these procedures for morbidly obese patients [12–15].

Another approach to treat obesity is by using anti-obesity medications (AOMs) as an adjunct therapy for those who fail to achieve a significant weight loss through lifestyle modification only. These medications can reduce body weight by decreasing food consumption or absorption, or increasing energy expenditure [16]. During the last decade, most new generation AOMs have shown encouraging tolerability profiles with a modest increase in the prevalence of use [17]. However, the shortfall of prolonged follow-up may confound the accurate ascertainment of risk–benefit; many AOMs that were presented as the solution to obesity have been withdrawn from the market during the last two decades owing to reports of multiple major AEs [18].

High-profile market withdrawals of AOMs justify the concerns about more serious AEs associated with the new generation of AOMs. In 1997, two AOMs (fenfluramine and dexfenfluramine) were withdrawn from the market due to concerns over valvular heart disease and pulmonary hypertension [19]. In 2010, the Food and Drug Administration (FDA) asked Abbott Laboratories to pull the anti-obesity medication sibutramine from the market in view of clinical trial data showing an increased risk for cardiovascular disease (CVD), specifically heart attack and stroke in high-risk cardiac patients [20, 21]. Recently, on February 13, 2020, the FDA requested a withdrawal of another AOM (lorcaserin) because a safety clinical trial revealed a potential risk of an increased cancer occurrence among lorcaserin users [22].

The available literature suggests the need for further investigation regarding the frequency of AEs associated with AOMs in order to assess the potential negative consequences of their use [23–25]. The spontaneous AE reports are considered a highly valuable source of information about serious, rare, or unknown AEs associated with medication use that was not recognized at the time of marketing [26]. It has been considered a primary resource for drug safety surveillance that continuously collects AE reports from patients and healthcare providers and has been identified as a fundamental tool for pharmacovigilance that reveals the realities of the clinical practice [27, 28].

Aim

With all consideration above, we proposed to explore and characterize the AEs attributable to the use of the AOMs and investigate previously unreported potential AEs associated with AOMs in the United States.

Ethics approval

This work was conducted in accordance with the ethical standards laid out in the Declaration of Helsinki, 1964. Because this study was an observational study using a global open database with anonymized information and not involving treatment intervention or collection of human samples, informed consent was exempted, and formal ethics approval was not required.

Method

Study design and source data

This study was designed as a retrospective, descriptive analysis of all reported AEs associated with AOMs using the FDA Adverse Event Reporting System (FAERS). Our study period covered from the first quarter of 2013 to the second quarter of 2020. FAERS is a de-identified publicly available database that includes information on AEs and medication error reports submitted by healthcare professionals, consumers, and manufacturers to the FDA. FAERS database is

meant to assist the FDA's post-marketing safety surveillance program for medications and therapeutic biologic products. The informatic formation of the FAERS database complies with the international safety reporting guidance declared by the International Conference on Harmonisation (ICH E2B) [29]. Medication errors and AEs are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Measures

All of the adverse event reports of the studied medications during the study were included for patients aged ≥ 18 years who have an AE report linked to one of the six major FDA approved AOMs listed in Table 1 [30]. The database were searched using both brand and generic names for every medication, based on the primary adverse event drug name. All AEs were extracted from the column of "preferred_term or PT" in the FAERS database, and we did include all adverse event terms extracted from FAERS and did not exclude any terms that may not match the MedDRA preferred terms. To exclude clinical indications other than obesity, we require either the indication to be for anti-obesity or using the brand name of the drugs, as clinical indication for obesity is brand-specific. Moreover, AEs were grouped and categorized according to their clinical similarities, such as CVD (cardio, heart, vascular, arithmetic, etc.), cancer (malignant, neoplasm, etc.), kidney injury (kidney, renal, AKF, etc.), and so on. The total numbers of AOMs adverse event reports, mean age, gender, cases, adverse reactions and outcomes were calculated by adding the data for all years for each AOM, and expressed as counts and percentages. The frequency for each major AE and outcome was calculated and tabulated for each studied drug (Tables 2 and 3). These adverse event outcomes are not jointly exclusive, so a patient can encounter more than one of these outcomes simultaneously. All analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2020 (Microsoft Corporation, Redmond, WA, USA).

Results

Using FAERS in the period between the first quarter of 2013 and the second quarter of 2020, we found 18,675 unique adverse event reports submitted to FAERS and associated with AOMs use, representing 15,143 patients, as one patient might have more than one report. Figure 1 shows the trends of AOMs reports over the study period, considering that only the first two quarters of 2020 were included. Among all reports, the mean age was 49.8 years [SD 1.83], while most patients were female (accounted for 73.4% of all cases).

The leading events associated with the AEs reported outcomes (Fig. 2) are nausea and vomiting with a total of 3,691 reports (Table 2), followed by dizziness and headache (3,540 reports), drug ineffectiveness or weight increased (2,647 reports), CVD (1,765 reports), acute kidney failure (AKF) /kidney injury (1,327 reports), diarrhea (988 reports), constipation (904 reports), insomnia (788 reports), anxiety (766 reports), dry mouth (626 reports), paraesthesia (481 reports), and cancer (194 reports). Cardiovascular AEs were mentioned in 542 reports (31%) for phentermine, 402 reports (23%) for liraglutide, 381 reports (22%) for phentermine/topiramate, 177 reports (10%) for orlistat, and 135 reports (8%) for lorcaserin (Table 2). It is apparent from this table that compared to the other AOMs, phentermine, phentermine/topiramate, and liraglutide had a relatively high number of reporters associated with AKF/kidney injury: 38%, 23%, and 17%, respectively. Top AEs associated with using naltrexone/bupropion drug were nausea and vomiting (27%), dizziness and headache (22%), insomnia (19%), and anxiety (17%).

The FAERS database had 21,229 unique reported outcomes involving the usage of AOMs. This includes 7,426 (35%) initial or prolonged stay hospitalization as the most

Table 1 Anti-obesity medications marketed in the United States from 1980 to 2020 [30, 41, 47, 53]

Generic name	Brand name	FDA approval date	Manufacturer
Orlistat	Xenical®	04/23/1999	CHEPLAPHARM
	Alli®	02/07/2007	GLAXOSMITH-KLINE CONS
Lorcaserin[a]	Belviq®	06/27/2012	EISAI INC
	Belviq-XR®	07/15/2016	EISAI INC
Phentermine	Adipex-P®	10/22/1980	TEVA
	Lomaira®	09/12/2016	AVANTHI INC
Phentermine/topiramate	Qsymia®	07/17/2012	VIVUS
Naltrexone/bupropion	Contrave®	09/10/2014	NALPROPION
Liraglutide	Saxenda®	12/23/2014	NOVO

[a]Withdrawn from the market in February 2020

Table 2 The most commonly reported adverse events associated with anti-obesity medications. Using FAERS databases 2013–2020

Drug names	Nausea and vomiting (%)	Dizziness and headache (%)	Drug ineffective/weight increased (%)	CVD (%)	AKF/Kidney Injury (%)	Diarrhea (%)	Constipation (%)	Insomnia (%)	Anxiety (%)	Dry mouth (%)	Paraesthesia (%)	Cancer (%)
Orlistat	101 (3)	147 (4)	231 (9)	177 (10)	160 (12)	174 (18)	34 (4)	20 (3)	24 (3)	5 (1)	25 (5)	13 (7)
Lorcaserin	283 (8)	906 (26)	864 (33)	135 (8)	69 (5)	67(7)	109 (12)	69 (9)	51 (7)	87 (14)	28 (6)	31 (16)
Phentermine	818 (22)	793 (22)	423 (16)	542 (31)	502 (38)	205 (21)	281 (31)	312 (40)	298 (39)	267 (43)	179 (37)	51 (26)
Phentermine/topiramate	377 (10)	416 (12)	302 (11)	381 (22)	307 (23)	106 (11)	121 (13)	194 (25)	184 (24)	133 (21)	138 (29)	22 (11)
Naltrexone/bupropion	1005 (27)	767 (22)	322 (12)	128 (7)	59 (4)	142 (14)	117 (13)	149 (19)	127 (17)	88 (14)	47 (10)	13 (7)
Liraglutide	1107 (30)	511 (14)	505 (19)	402 (23)	230 (17)	294 (30)	242 (27)	44 (6)	82 (11)	46 (7)	64 (13)	64 (33)
Total	3691	3540	2647	1765	1327	988	904	788	766	626	481	194

Percentage in each cell calculated for each adverse event by column

CVD cardiovascular disease, *AKF* acute kidney failure

frequently reported outcome, 1613 (7.6%) life-threatening events, 1039 (4.9%) deaths, 1249 (5.9%) disability, 671 (3.2%) congenital anomaly, and 517 (2.4%) required intervention to prevent permanent impairment/damage (Table 3). Death and life-threatening outcomes represented 15% of the documented serious AEs associated with phentermine/topiramate medication use, 14% of liraglutide use, and 13% of lorcaserin and 12% of phentermine use (Table 3). The largest number of fatal cases was reported for phentermine (n = 331), followed by liraglutide (n = 217) and phentermine/topiramate (n = 174).

Discussion

A retrospective descriptive study of the adverse events following AOMs use from 2013 through 2020 was conducted using FAERS data in the US pharmaceutical market. Due to the inherent limitations in the clinical trial studies, such as limited follow-up duration, stringent design, and relatively small sample size, the spontaneous reporting system (SRS) has been used in pharmacovigilance for safety assessment of a suspected drug's AEs. Furthermore, SRS plays a integral part in signal identification, and the FDA has developed the FAERS database for postmarketing surveillance to monitor the safety of drugs and improve public health [31]. This study aimed to describe the most common AEs and investigate previously unreported potential AEs associated with using AOMs.

To our knowledge, this is the first study that has systematically analyzed AEs reported for AOMs located in a nationally representative database for over a 7-year period. Over 73% of the reported AEs affected female adults, and that is consistent with previous studies that analyzed global AE reporting patterns of the AOMs [32, 33]. However, because the FAERS database only provides AEs cases (positive and false-positive cases) and does not provide the number of patients who took the medication without reporting any AE, we cannot infer whether this can be explained by the increased risk of the incidence of AEs in this population. Drug ineffectiveness, dizziness, headache, nausea, vomiting, and diarrhea were among the most frequently reported AEs for all reports recorded in the FAERS database through 2002 [34], and that is consistent with our findings. Compared to the other studied medications, the percentage of cardiovascular and AKF/ kidney injury AEs were sizable among phentermine, liraglutide, and phentermine/topiramate users (Table 2).

For liraglutide, which is the only injectable formulation of the AOMs, many AEs of the type of gastrointestinal disorders, cancer, and CVD were found. A relatively high rate of deaths and life-threatening cases were observed with using liraglutide. Additionally, a relatively high percentage

Table 3. Type of hospitalization associated with anti-obesity medications. Using the FDA's Adverse Event Reporting System (FAERS) database 2013–2020

Drug names	Hospitalization—initial or prolonged	Life-threatening	Death	Disability	Congenital anomaly	Required intervention to prevent permanent impairment/damage	Other
Orlistat (%)	835 (39)	152 (7)	89 (4)	104 (5)	56 (3)	44 (2)	841 (40)
Lorcaserin (%)	945 (37)	193 (8)	137 (5)	171 (7)	44 (2)	39 (2)	1004 (40)
Phentermine (%)	2452 (37)	481 (7)	331 (5)	362 (5)	237 (4)	175 (3)	2627 (39)
Phentermine/topiramate (%)	962 (32)	260 (9)	174 (6)	262 (9)	176 (6)	98 (3)	1114 (37)
Naltrexone/bupropion (%)	804 (30)	151 (6)	91 (3)	163 (6)	39 (1)	48 (2)	1403 (52)
Liraglutide (%)	1428 (34)	376 (9)	217 (5)	187 (4)	119 (3)	113 (3)	1725 (41)
Total (%)	7426 (35)	1613 (7.6)	1039 (4.9)	1249 (5.9)	671 (3.2)	517 (2.4)	8714 (41)

Percentage in each cell calculated for each drug by row.

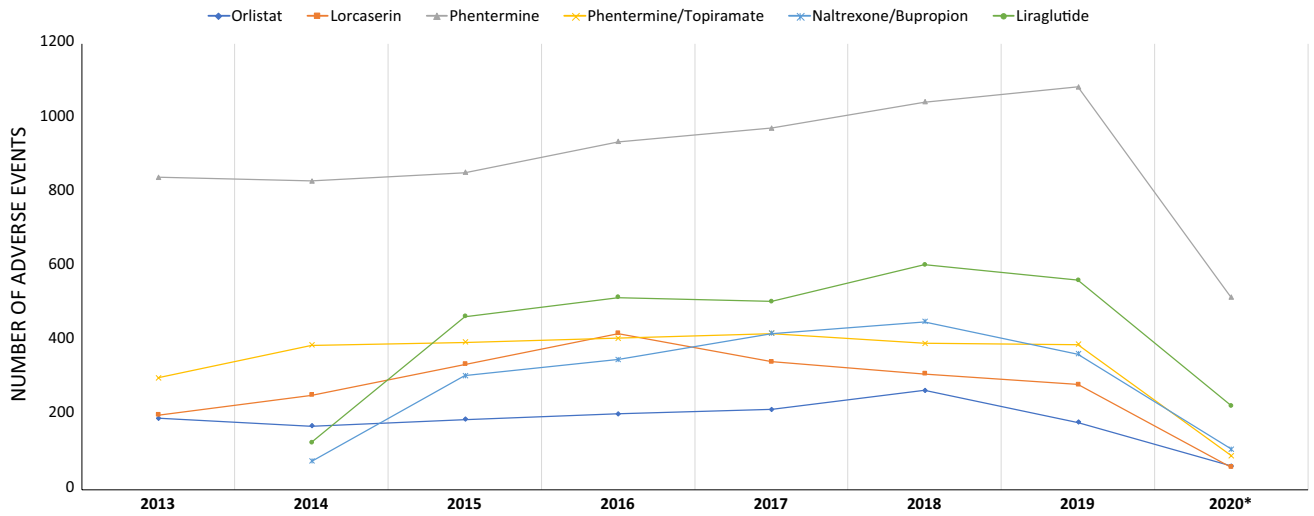

Fig. 1 Trends of anti-obesity medications reported adverse events: United States, first quarter of 2013 – second quarter of 2020, using the FDA's Adverse Event Reporting System (FAERS) database. *Only the second quarter of 2020 is included

of disability reports and common gastrointestinal disorders were at the top of the AEs associated with naltrexone/bupropion medication. A previously published systematic review and meta-analysis study [35] stated that compared with placebo, among the FDA-approved AOMs, the odds of adverse event-related treatment discontinuation was the highest among liraglutide users (odds ratio (OR); 2.95) followed by naltrexone-bupropion users (OR; 2.64).

Unlike the other medications, orlistat works by decreasing fat absorption through inhibiting gastric and pancreatic lipase and expelling dietary fat through the bowels, [36] while the other five medications work mainly through CNS pathways that either enhance satiety or reduce appetite. This explains why a large number of diarrhea, renal complications, and drug ineffectiveness AEs were reported with orlistat. Our findings were consistent with previous studies found that the most common AEs leading to withdrawal for orlistat were gastrointestinal disorders and renal complications [37–39]. Death represents 4% of the reported AEs attributed to orlistat (Alli®), and since it is the only over-the-counter weight loss pill approved by the FDA [40], the marketing authorization holder should further investigate the fatal cases potentially associated with using this medication.

Phentermine anti-obesity monotherapy is approved for adults for 90-day use and contraindicated in patients with a history of CVD [41]. It is still the most commonly prescribed AOM in the USA and worldwide, except in the European Union due to its potential adverse effects [42]. From the data shown in Table 2, it is apparent that CVD, AKF/kidney injury, paraesthesia, dry mouth, constipation, and insomnia are highly prevalent among phentermine and phentermine/topiramate users, which is consistent with previous studies

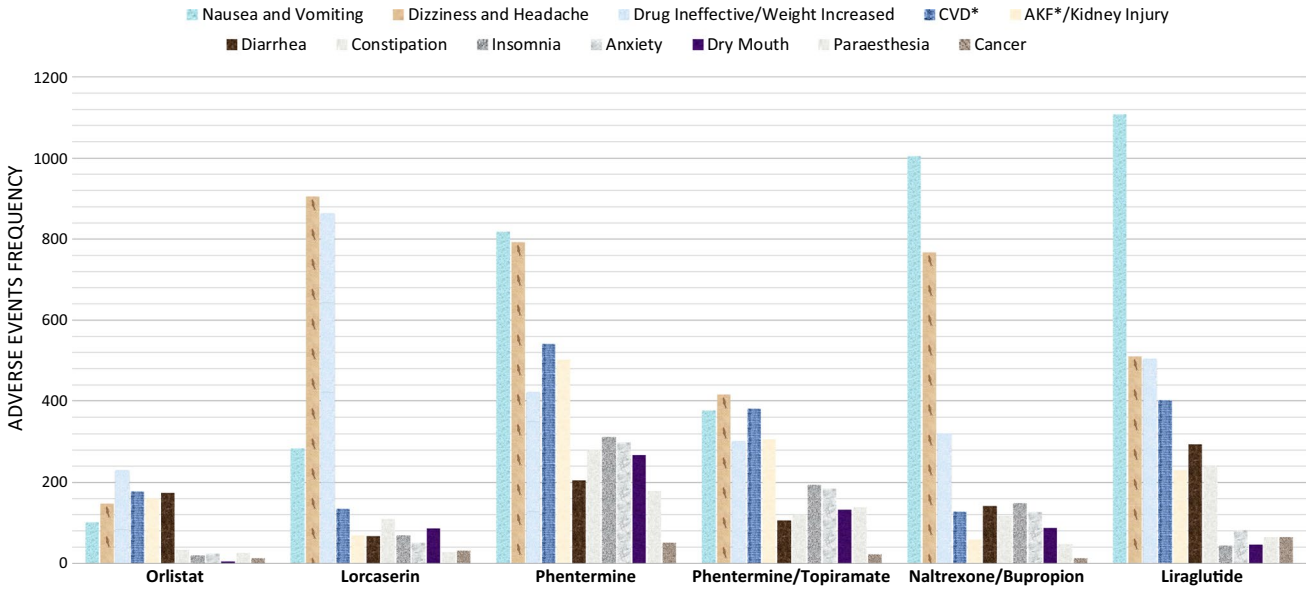

Fig. 2 The most common reported adverse events associated with anti-obesity medications: Using the FDA's Adverse Event Reporting System (FAERS) database 2013–2020. *CVD, cardiovascular disease. AKF, acute kidney failure

[43–45]. Figure 3 reveals a considerably high frequency of the congenital anomaly type of hospitalization associated with phentermine/topiramate. A fetal safety issue and teratogenicity concerns related to phentermine/topiramate use was expressed by the FDA owing to the risk of increased oral clefts. Consequently, women of childbearing age are advised on contraceptive planning before using this medication [46–48].

Drug ineffectiveness, dizziness, headache, and dry mouth were among the most common AEs associated with lorcaserin. Compared to the other medications, the CVD-related AEs were relatively low (8%) as the medication showed a low rate of major cardiovascular events in previously published studies [41, 46, 49]. In February 2020, the drug was withdrawn from the market over the potential risk of an increased cancer occurrence. Our analysis revealed that cancer reports denote less than 0.9% of the overall lorcaserin submitted reports and represent 16% of the overall cancer reports associated with the studied medications, considering that not the only primary suspected medications were included. Rekha Kumar and Donna Ryan wondered whether lorcaserin withdrawal, owing to a numerical imbalance in the cancer cases occurring in a large, 12,000 participants clinical trial, has left more questions than answers. Ascertainment bias was among many concerns that led them to request a full disclosure of more information around the lorcaserin/cancers potential risk association [50].

The majority of serious AEs were found for phentermine, liraglutide, phentermine/topiramate and they were of the type 'cardiac' and 'renal' disorders. The proper use of medication through following the pharmacist's or the physician's instructions can significantly reduce undesirable effects. To ascertain whether these findings have contributed to detecting new AE signals or merely affirming existing knowledge, conducting comparative studies of the reported AE information with the AEs posted on the official product label are required.

These data must be interpreted with caution because there is no ultimate proof of the causal relationship between exposure to a drug and the reported event. Furthermore, because of the duplicate and incomplete reports (unknown denominator), the incidence of AEs cannot be estimated using FAERS data. Consequently, since we did not limit our analysis to the only primary suspected medications, the values only provide safety signals and do not denote a real risk. Additionally, there is a potential for bias based on physician preference when prescribing the appropriate choice of the AOM for a patient or when reporting the AE. Besides, comorbidities or concomitant drugs might confound the association between a drug and an AE [51]. Also, some medications have other uses that might confound the analysis, particularly liraglutide which is an increasingly common medication used for type 2 diabetes mellitus [52]. To overcome this limitation, we require either the indication to be for anti-obesity or using the brand name of the medication. Ultimately, these limitations may lead to an inflation of the risks attributable to the AOMs.

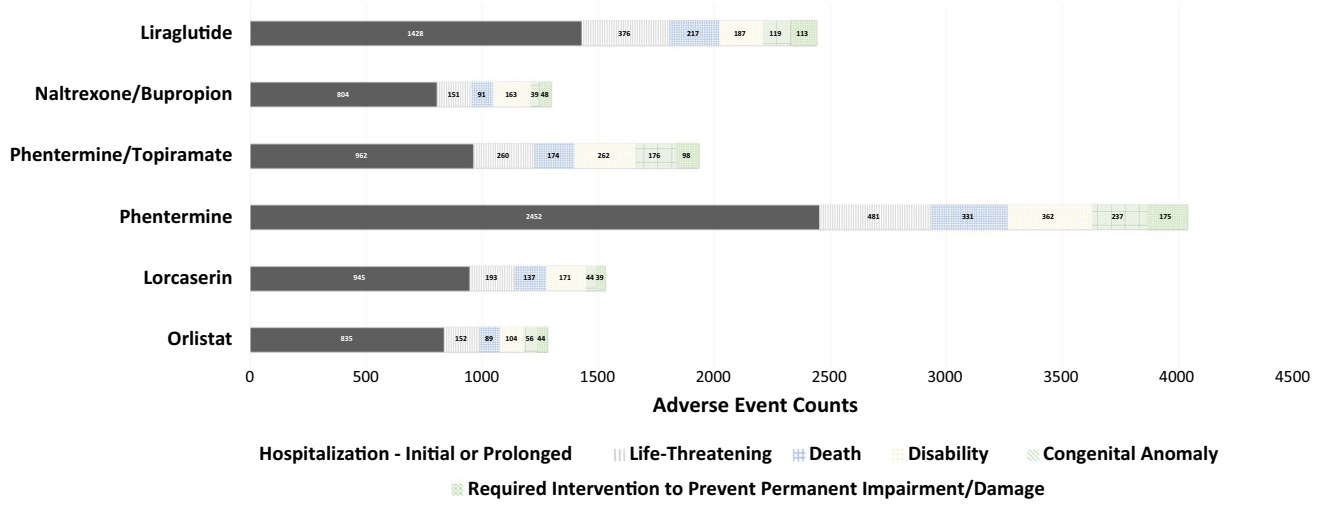

Fig. 3 Trends of the type of hospitalization associated with anti-obesity medications: Using the FDA's Adverse Event Reporting System (FAERS) database 2013–2020

Conclusion

Given the variation between individuals in their response to the AOMs, the pharmacotherapeutic use of the agents/drugs continues to be a challenge; as such, it is essential to continue and systematically observe AOMs' safety to optimize their use. Using the FAERS database, we found that nausea and vomiting were the most frequent events associated with the AEs reported outcomes. Moreover, more severe AEs in the type of CVD, AKF /kidney injury were among the most commonly reported AEs. Also, this study revealed that 35% of the reviewed AE reports required an initial or prolonged hospitalization. Therefore, healthcare providers should be aware of the potential AEs attributed to the use of AOMs.

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