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Article

Is There a Risk for Semaglutide Misuse? Focus on the Food and Drug Administration-FDA Adverse Events Reporting System (FAERS) Pharmacovigilance Dataset

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Abstract: Recent media reports commented about a possible antidiabetics' misuse issue related to molecules promoted as a weight-loss treatment in non-obese people. We evaluated here available pharmacovigilance misuse/abuse signals related to *semaglutide*, a glucagon-like peptide-1 (GLP-1) analogue, in comparison to other GLP-1 receptor agonists (*albiglutide*; *dulaglutide*; *exenatide*; *liraglutide*; *lixisenatide*; *tirzepatide*) and the *phentermine-topiramate* combination. To that aim, we analysed the Food and Drug Administration-FDA Adverse Events Reporting System (FAERS) dataset, performing a descriptive analysis of adverse event reports (AER) and calculating related pharmacovigilance measures, including the reporting odds ratio (ROR) and the proportional reporting ratio (PRR). During January 2018-December 2022, a total of 31,542 AER involving the selected molecules were submitted to FAERS; most involved dulaglutide (n=11,858; 37.6%) and semaglutide (n=8,249; 26.1%). In comparing semaglutide vs the remaining molecules, the AER 'drug abuse', 'drug withdrawal syndrome', 'prescription drug used without a prescription' and 'intentional product use issue' respective PRR values were 4.05, 4.05, 3.60 and 1.80 (all<0.01). The same comparisons of semaglutide vs the phentermine-topiramate combination were not associated with any significant differences. To the best of our knowledge, this is the first study documenting the misusing/abusing potential of semaglutide in comparison with other GLP1 analogues and the phentermine-topiramate combination. Current findings will need to be confirmed by further empirical investigations to fully understand the safety profile of those molecules.

Keywords: semaglutide; drug misuse; drug abuse; pharmacovigilance; image- and performance-enhancing (IPED) drugs; glucagon-like peptide-1 (GLP-1) agonists

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is a chronic and progressive illness [1]. In parallel with this, the worldwide prevalence of obesity, a key target in the treatment and prevention of diabetes [2], has been progressively increasing over the past few decades and is predicted to continue to rise in coming years. However, lifestyle modification, including dietary changes and physical exercise, are often insufficient to achieve clinically meaningful weight loss due to physiological mechanisms that limit weight reduction and promote weight regain [3].

In the absence of contraindications, metformin has traditionally been considered as the first-line medication in T2DM patients; however, it promotes modest weight reduction [4,5]. Conversely, the invasive bariatric surgery has been the primary approach to treat severely obese individuals. More recently, the emergence of agents impacting on the brain satiety centres' function may provide effective, non-invasive, treatment of obesity for individuals with and without diabetes. The long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide, and tirzepatide, a dual-agonist at both the receptors for glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP), are now approaching the success seen with bariatric surgery; in association with these molecules, a decreasing body weight (e.g. by >10% in most patients), with a favourable safety profile is being observed [2,6–8]. Indeed, tirzepatide showed even better dose-dependent efficacy (e.g. greater reduction in haemoglobin A1c/HbA1c and body weight) than placebo; basal insulin; and the two GLP-1 analogues dulaglutide and semaglutide as well [6,9–14]. The principal role of the incretins GIP and GLP-1 has generally been thought to stimulate insulin secretion. GLP-1 improves fasting blood glucose due to its direct action on pancreatic islets and decreases postprandial hyperglycaemia due to inhibition of gastric emptying and thus reducing levels of glucose entry into the circulation. GIP directly stimulates insulin secretion through the β cell GIP receptors. Indirectly, GIP potentiates α cell activity to enhance α to β cell communication through the GLP-1R/glucagon receptor (GcgR), thus indirectly stimulating insulin secretion through the α cell [15]. Among other incretin mimetics, both liraglutide, at a maximum daily dose of 3.0 mg, and semaglutide, at a maximum weekly maintenance dose of 2.4 mg, have already received the regulatory approval for the treatment of obesity, whilst tirzepatide is currently being assessed for this indication [10,16]. In the United Kingdom (UK), semaglutide received the approval as a weight loss medication to be prescribed on the National Health System (NHS) as of March 2023 [17]. With these medications, a range of gastrointestinal adverse effects have been reported, e.g. nausea and diarrhoea [18]; conversely, severe hypoglycaemia, fatal adverse events, acute pancreatitis, cholelithiasis, and cholecystitis are considered as rare events [1,8].

Is there a GLP-1 analogues' misusing issue?

Classical medications for obesity management can be typically divided into a few groups: opiate antagonists (naltrexone); pro-dopaminergic drugs (bupropion, phendimetrazine, benzphetamine, diethylpropion, and phentermine), fat blockers (orlistat), the antihyperglycaemic drug metformin; the serotonin 2C receptor agonist lorcaserin, the serotonin and norepinephrine reuptake inhibitor sibutramine, and the selective cannabinoid receptor-1 blocker rimonabant, which was lately dismissed from the market for severe human health risks, e.g. psychiatric side effects, especially depression and suicide [19]. Because of their misusing potential, some of these molecules are classified as controlled substances, e.g., lorcaserin and sibutramine are both classified as Schedule IV controlled drugs under the Controlled Substances Act [19,20]. Similarly, because of phentermine relationship with amphetamine, it was determined to have the potential for abuse and designated as a Schedule IV controlled substance [21]. Thus, used in combination with topiramate, both synergism and efficacy should be improved, with side effects and potential misuse being possibly reduced [22]. In the case of metformin, it has been associated with levels of both diversion [23] and abuse [24], having been ingested either at high dosages [25], or by eating disorder individuals [26].

A large range of newspapers' [27] reports commented about the possible existence of semaglutide and other GLP-1 analogues' misusing issue. In line with this, in March 2023 the French National Agency for Drug Safety announced 'enhanced surveillance' levels for semaglutide. In fact,

since September 2022, the drug agency had been alerted by both a range of videos on social media and by pharmacists reporting forged prescriptions and use for weight loss in non-diabetics [28]. Social media platforms' semaglutide promotion as a weight-loss treatment [29], and the associated increase in demand, may well have contributed to an ongoing worldwide shortage of the drug [29–31]. One could hypothesize that the non-realistic versions of physical attractiveness being promoted for otherwise healthy, non-obese, people may be behind these putative misusing levels. The issue can be facilitated by a putative medications' acquisition from rogue websites [32,33].

In contrast with the above, it is of interest that by the time of drafting of this paper no literature reports focussing on semaglutide and novel antidiabetics' misusing issues appeared to have been published. Hence, we aimed here at determining the available pharmacovigilance misuse/abuse signals relating to *semaglutide* versus other incretin mimetics such as the following molecules, *albiglutide*; *dulaglutide*; *exenatide*; *liraglutide*; *lixisenatide*; *tirzepatide*; and the combination *phentermine-topiramate*, analysing the Food and Drug Administration-FDA Adverse Events Reporting System (FAERS) dataset.

2. Results

From January 2018 to December 2022, a total of 31,542 adverse event reports (AER) involving the selected molecules were submitted to FAERS. Among these, 37.6% involved dulaglutide (n=11,858), 26.1% semaglutide (n=8,249), 25.0% liraglutide (n=7,883), 8.2% exenatide (n=2,585), 1.24% lixisenatide (n=390), 0.9% tirzepatide (n=290), 0.6% phentermine-topiramate (n=183), and 0.3% albiglutide (n=104). Regarding semaglutide, during the selected timeframe an increase in the number of reported AER compared to remaining molecules was here observed (Figure 1); overall, most reports came from the United States of America (USA) and involved female adults (Table 1).

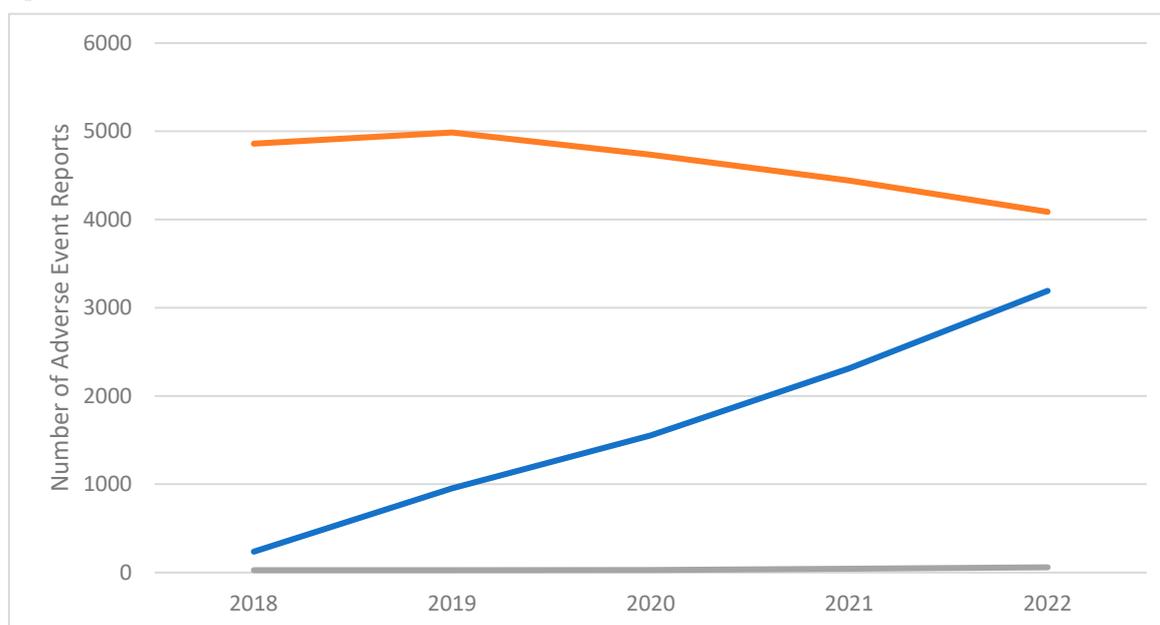


Figure 1. Number of Adverse Event Reports (AER) involving semaglutide, other glucagon-like peptide-1 (GLP-1) analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) and the combination phentermine-topiramate. Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022). LEGEND: Semaglutide: blue colour; Other GLP-1 analogues: orange; Phentermine-topiramate: grey.

Table 1. Demographics related to Adverse Events (AER) typically reported for semaglutide; phentermine-topiramate; and other other glucagon-like peptide-1 (GLP-1) analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide). Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

Number of AER (%)	Overall	Semaglutide	Phentermine-Topiramate	Other GLP-1 analogues*
Mean Age, years (SD)	61.0 (19.2)	60.2 (13.7)	49.9 (14.7)	61.4 (20.8)
Females	16559 (53%)	4470 (54%)	156 (85%)	11933 (52%)
Males	12986 (41%)	3449 (42%)	22 (12%)	9515 (41%)
Concomitant substances (%)				
Alcohol	23 (0.1%)	2 (0.0%)	0 (0.0%)	21 (0.0%)
Cannabis	33 (0.1%)	13 (0.2%)	0 (0.0%)	20 (0.0%)
Cocaine	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Opioids	1712 (5.4%)	249 (3.0%)	16 (8.7%)	1447 (8.7%)
Amphetamines	25 (0.1%)	9 (0.1%)	1 (0.0%)	16 (0.1%)
Benzodiazepines	1550 (4.9%)	238 (2.9%)	17 (9.3%)	1295 (5.6%)
Country of origin	USA 19664(62.0%) France 1729 (6.0%) Canada 1562 (5.0%)	USA 5016 (71.0%) Canada 825 (10.0%) United Kingdom 360 (4.0%)	USA 173 (95%) Korea 9 (5.0%) Not specified (0.0%)	USA 14475 (62.0%) France 1449 (6.0%) Japan 1078 (5.0%)

Abbreviations: AER: Adverse Event Report; GLP-1-RA: glucagon-like peptide-1 receptor agonists; SD: standard deviation; USA: United States of America. *This combines albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and tirzepatide.

Most of the AERs recorded for semaglutide were related to gastrointestinal issues; an off-label medication use was here recorded only for semaglutide (483/8,249 cases; 5.85%) (Table 2).

Table 2. Most typically reported semaglutide; phentermine-topiramate; and other other glucagon-like peptide-1 (GLP-1) analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) Adverse Event Reports (AER). Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

SEMAGLUTIDE		PHENTERMINE-TOPIRAMATE		OTHER GLP-1 analogues*	
Preferred Term	# AER (%)	Preferred Term	# AER (%)	Preferred Term	# AER (%)
Nausea	1,047 (13%)	Nephrolithiasis	14 (8%)	Nausea	1,843 (8%)
Vomiting	921 (11%)	Headache	11 (6%)	Blood glucose increased	1,604 (7%)
Diarrhoea	699 (8%)	Weight increased	10 (5%)	Vomiting	1,586 (7%)
Pancreatitis	492 (6%)	Angle closure glaucoma	9 (5%)	Pancreatitis	1,459 (6%)
Off label use	483 (6%)	Blurred vision	9 (5%)	Diarrhoea	1,426 (6%)
Weight decreased	465 (6%)	Suicidal ideation	8 (4%)	Acute kidney injury	1,112 (5%)

Blood glucose increased	424 (5%)	Chronic kidney disease	7 (4%)	Weight decrease	1,082 (5%)
Decreased appetite	387 (5%)	Hypoesthesia	7 (4%)	Fatigue	794 (3%)
Fatigue	357 (4%)	Breast cancer	6 (3%)	Decreased appetite	711 (3%)
Dehydration	352 (4%)	Paraesthesia	6 (3%)	Chronic kidney disease	689 (3%)

Note that multiple preferred terms can be listed in an Adverse Event Report. *Abbreviations:* AER: Adverse Event Report; GLP-1: glucagon-like peptide. *This combines albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and tirzepatide.

In terms of reported outcomes by drug, semaglutide was associated with fatalities in 273/8,249 (3.3%) of AER, whilst this event occurred with the remaining molecules in 1,705/23,110 (7.4%) of AER (Table 3).

Table 3. Most typically reported semaglutide; phentermine-topiramate and other other glucagon-like peptide-1 (GLP-1) analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide). Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

Semaglutide	Phentermine-topiramate		Other GLP-1 analogues*		
Outcome	# AER (%)	Outcome	# AER (%)	Outcome	# AER (%)
Other outcomes	5418 (66%)	Other outcomes	154 (84%)	Other outcomes	14206 (61%)
Hospitalized	3479 (42%)	Hospitalized	46 (25%)	Hospitalized	10287 (45%)
Life threatening	306 (4%)	Disabled	14 (8%)	Died	1705 (7%)
Disabled	299 (4%)	Life threatening	3 (2%)	Life threatening	1103 (5%)
Died	273 (3%)	Died	1 (1%)	Disabled	671 (3%)
Required intervention	67 (1%)	Required intervention	1 (1%)	Required intervention	76 (<1%)

Note that multiple outcomes can be listed in an Adverse Event Report. *Abbreviations:* AER: Adverse Event Report; GLP-1: glucagon-like peptide-1. *This combines albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and tirzepatide.

2.1. Pharmacovigilance signals

Drug misuse-; abuse-; and withdrawal-related AER were here most typically re-ported for semaglutide compared with the other GLP-1 analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) selected and the combination phentermine-topiramate (Table 3). Specifically, 'drug abuse', 'drug withdrawal syndrome' and 'prescription drug used without a prescription' were reported more >3.50 times as frequently (e.g. PRR values were 4.05, 4.05, and 3.60, respectively; FDR<0.01), and 'intentional product use issue' was reported almost two times as frequently (PRR= 1.80; FDR<0.01) (Table 4). Conversely, no significant differences in terms of the selected AER occurrence were here identified when comparing semaglutide vs the phentermine-topiramate combination.

Table 4. Signal scores regarding drug misuse; abuse; and withdrawal-related AER for: semaglutide; other other glucagon-like peptide-1 (GLP-1) analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) and the phentermine-topiramate combination. Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

PT (MedDRA)	SEMAGLUTIDE VS. OTHER GLP-1 analogues				SEMAGLUTIDE VS. PHENTERMINE-TOPIRAMATE			
	PRR (FDR)	ROR (FDR)	IC025 (FDR)	EB05 (FDR)	PRR (FDR)	ROR (FDR)	IC025 (FDR)	EB05 (FDR)
Accidental overdose	0.59 (0.60)	0.59 (0.60)	-1.62 (0.34)	0.50 (0.41)	Inf (<0.01)	Inf (<0.01)	-1.41 (0.50)	0.99 (0.52)
Drug abuse	4.05 (<0.01)	4.05 (<0.01)	-0.63 (0.16)	0.80 (0.12)	Inf (<0.01)	Inf (<0.01)	-1.74 (0.52)	0.99 (0.53)
Drug level increased	0.85 (0.46)	0.85 (0.46)	-1.12 (0.27)	0.62 (0.29)	Inf (<0.01)	Inf (<0.01)	-1.21 (0.49)	0.99 (0.52)
Drug withdrawal syndrome	4.05 (<0.01)	4.05 (<0.01)	-0.63 (0.16)	0.80 (0.12)	Inf (<0.01)	Inf (<0.01)	-1.74 (0.52)	0.99 (0.53)
Incorrect route of product administration	0.55 (0.61)	0.55 (0.61)	-1.65 (0.34)	0.48 (0.42)	Inf (<0.01)	Inf (<0.01)	-1.34 (0.50)	0.99 (0.52)
Intentional product misuse	0.42 (0.64)	0.42 (0.64)	-1.68 (0.35)	0.40 (0.45)	0.32 (<0.01)	0.32 (<0.01)	-1.01 (0.48)	0.99 (0.53)
Intentional product use issue	1.80 (<0.01)	1.80 (<0.01)	0.08 (<0.01)	1.11 (<0.01)	Inf (<0.01)	Inf (<0.01)	-0.54 (0.41)	0.99 (0.50)
Overdose	0.92 (0.46)	0.92 (0.46)	-0.66 (0.17)	0.72 (0.19)	Inf (<0.01)	Inf (<0.01)	-0.71 (0.44)	0.99 (0.51)
Prescription drug used without a prescription	3.60 (<0.01)	3.60 (<0.01)	-0.42 (0.10)	0.85 (0.08)	Inf (<0.01)	Inf (<0.01)	-1.50 (0.51)	0.99 (0.53)
Substance use	Inf (0.70)	Inf (0.70)	-0.29 (0.06)	0.91 (0.04)	Inf (0.04)	Inf (0.04)	-1.74 (0.53)	0.99 (0.53)

Boldface denotes significance at FDR<0.05; Signal scores for drug-event pairs less than 5 are not shown. *Abbreviations:* EB05: Bayesian empirical geometric mean (lower 5th percentile of the posterior observed-to-expected distribution); FDR: false discovery rate; GLP-1: glucagon-like peptide-1; IC025: information component; the IC025 value is the lower limit of a 95% credibility interval for the IC; MedDRA: Medical Dictionary for Regulatory Activities; PRR=proportional reporting ratio; PT: preferred terms; ROR: reporting odds ratio.

3. Discussion

To the best of our knowledge, this is the first study documenting the misuse and abuse potential of semaglutide in comparison with both remaining GLP-1 analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) and the phentermine-topiramate combination. The comparison was here carried out with the help of a range of worldwide, valuable [34,35], pharmacovigilance data, as those derived from the FAERS. AER related to semaglutide showed here steady and progressive increasing levels during the years 2018-2022; conversely, the phentermine-topiramate related AER remained roughly stable, and AER related to the remaining GLP-1 mimetics

appeared to have decreased during the same years. Consistent with this, in the years previous to the timeframe (i.e. 2018-2022) here considered, prescriptions for all the molecules selected increased, and this was especially true for those relating to liraglutide, dulaglutide, and semaglutide [36–39].

As expected, for both semaglutide and the other GLP-1 analogues most reported AER involved the gastrointestinal adverse events [40]. Conversely, the phentermine-topiramate AER most typically involved here dizziness, headache, blurred vision, hypoesthesia, and paraesthesia, which have all been reported for topiramate [41]; in relation to the AER registered for the phentermine/topiramate combination, it is interesting that no significant data on misuse/abuse are reported, despite clinicians' concerns regarding the use of single phentermine [21,22]. Given both the low risk of semaglutide severe adverse events (e.g. mostly mild-to-moderate and transient), and its beneficial metabolic and cardiovascular actions [42–44], the molecule is considered to possess an overall favourable risk/benefit profile for patients with T2DM [43]. It may be a reason of concern, however, that an off-label prescription issue for semaglutide, but not for the remaining GLP-1 analogues, was here identified. This may happen when a drug is being used for an unapproved indication/population or at an unapproved dosage. Off-label use of a medication is at times associated with its misusing potential. In line with this, and in contrast with remaining GLP-1-RA, semaglutide appeared here to be associated with significantly higher levels of: i) abuse; ii) intentional product use issues; and iii) use without a prescription. To the best of our knowledge, this finding has never been reported before in the medical literature and is fully consistent with the vast range of anecdotal, unconfirmed, magazines and newspapers' reports [17,27,30,31].

Semaglutide and GLP-1RA as image- and performance-enhancing drugs (IPED)

The phenomenon of drug misuse and abuse for weight-loss purposes has been frequently reported in the literature. Image- and Performance-Enhancing Drugs (IPEDs) include a wide range of drugs across various pharmacological categories misused to obtain an alteration/enhancement of physical performance or appearance [45] as it occurs with slimming products. A vast range of molecules have been misused as weight loss agents, especially relating to sympathomimetic agents, e.g., amphetamine/methamphetamine type drugs; ecstasy; and cocaine [46]. Other extreme slimming misusing agents have included: β -2 agonists such as clenbuterol [47]; diuretics [48]; and dinitrophenol/DNP [49]. Overall, these agents are being misused and abused by vulnerable; non-obese; body dysmorphic; subjects for their image- enhancing [50], significant slimming, potential. From this point of view, semaglutide may possess the potential of being misused as a weight loss, IPED, agent. Phentermine is one of the medications being considered by obesity specialists for weight loss purposes [19]. Whilst phentermine has not been previously associated with evidence of physical dependence or addiction [51], it may well possess a potential of misuse [52]. This may explain the lack of statistical differences, in terms of misuse/abuse-related AERs, when the phentermine-topiramate combination was here compared with semaglutide. Overall, the information provided by this study does not allow us to deduce explanations for the misuse of each individual substance but, on the basis of pharmacovigilance signals, to compare molecules with each other and provide useful information for clinicians and institutions to monitor possible side effects, adverse events and misuse. We can hypothesise that issues related to: the formulation (subcutaneous versus oral); drug availability and ease of prescription; pharmacokinetic and pharmacodynamic properties; as well as the effects on weight reduction (semaglutide and liraglutide would appear to be the most effective in the long term) of the individual drugs may explain the misuse of semaglutide in comparison with the other molecules under study.

Semaglutide and GLP-1RAs as molecules acting on the reward system?

One could wonder if there is a neurobiological issue putatively associated with the decreased appetite and improved levels of satiety [2,53], and hence with the significant weight loss, associated with GLP-1RA in general and semaglutide in particular. In the central nervous system (CNS), GLP-1Rs are expressed in several brain regions involved in the regulation of metabolism and energy balance [54]. The reward-related brain regions that regulate appetitive and consumption behaviours

include the mesolimbic regions' nucleus accumbens (NAc), ventral tegmental area (VTA) and amygdala [55,56], with GLP-1Rs being located in the mesolimbic system [57,58]. Furthermore, the gut-brain axis peptide ghrelin enhances dopamine release in the VTA [59]. Hence, one could wonder if the withdrawal symptoms here associated with semaglutide may be conceivably related with its activity on the reward system; this is consistent with a range of anecdotal Redditors' observations highlighting both rebound and craving phenomena after withdrawing from semaglutide [60]. In line with this, a recent randomized-controlled trial showed that 1 year after having withdrawn from a weekly semaglutide 2.4 mg treatment, participants regained two-thirds of their weight loss [61]. Indeed, GLP-1 analogues may reduce the *rewarding effects* of palatable food intake (for a review, see also [59]) and the food-related brain responses in both T2DM and obese subjects in insula, amygdala, putamen, and orbitofrontal cortex [62]. Consistent with these observations, GLP-1RA can reduce: cue- and drug-induced fentanyl seeking [63]; physical and behavioural effects of morphine withdrawal [58]; cue-, stress-, and drug-induced heroin-seeking [64]; use of cocaine, amphetamine, alcohol, and nicotine in animals when administered over several days or weeks [64–67]. In one randomized-controlled trial, exenatide, administered weekly in combination with nicotine replacement therapy, improved smoking abstinence, reduced craving and withdrawal symptoms, and decreased weight gain among abstainers [68]. Another study demonstrated that weekly exenatide significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients [69]. Therefore, GLP-1 RA are gaining increasing attention as new therapeutic agents for the treatment of reward system-related disorders [57].

The potential use of GLP-1 RA in neurology

Preclinical studies suggest that exenatide can normalise dopaminergic function, showing its potential protective action against cytokine mediating apoptosis and its substantial therapeutic utility in diseases where neuroinflammation may play a significant role, such as the Parkinson's disease (PD) [70], Alzheimer Disease (AD), diabetes, and strokes [71]. Consistently, exenatide administered weekly had positive effects on practically defined off-medication motor scores in PD, and this outcome was sustained beyond the period of exposure [72]. Interestingly, the GLP-1 RA exenatide in its extended-release formulation has been successfully employed to alleviate the motor symptoms of PD patients [73], a condition characterized by a deficit in dopaminergic neurotransmission, a critical axis of the reward system. Notably, in preclinical models of brain aging and neurodegeneration, the same compound has been shown to positively affect the signalling of the brain-derived neurotrophic factor (BDNF) and modulate synaptic plasticity [71,74], thereby introducing the possibility of long-lasting behavioural effects driven by long-term structural brain and neural modifications.

Limitations

Despite the interest of current findings, they may need to be interpreted with caution. First, although disproportionality analysis is a suitable tool for quantifying signs of drug abuse/misuse, it has a limited ability to differentiate the type or reason for abuse (e.g. recreational, self-medication, etc.). Furthermore, confounding factors such as comorbidities, dosages/routes of administration and concomitant drugs consumed cannot be adequately assessed with a pharmacovigilance approach. This is due to the inherent nature of the reports used as primary sources for the study, reflecting only the information provided to the FDA by the reporter. The study of AER alone is rarely sufficient to confirm that a certain effect in a patient was caused by a specific drug, as it may also have been caused by the disease treated, by a new disease developed by the patient or by another medicine the patient is taking. Indeed, the number of case reports for a particular drug or suspected adverse reaction does not only depend on the actual frequency of the adverse reaction, but also on the extent and conditions of use of the drug, the nature of the reaction, the related public awareness levels, and adherence to reporting. Notwithstanding the related limitations and biasing factors of pharmacovigilance studies based on spontaneous reporting, the PRR and remaining statistical values here identified should be interpreted as strong signals of disproportionality.

4. Materials and Methods

4.1. Data source

The present study focussed on the FAERS pharmacovigilance data in relation to semaglutide and other drugs within the same clinical indication and in the same drug group, including: albiglutide; dulaglutide; exenatide; liraglutide; lixisenatide; tirzepatide. Although not in the same drug class, the phentermine-topiramate combination, being used with the same indication (e.g. obesity), was here included. FAERS data were made available online through the FAERS Public Dashboard [75]. In pharmacovigilance, 'misuse' is being considered the intentional and inappropriate use of a product other than as prescribed or not in accordance with the authorized product information, whilst 'abuse' is the intentional non-therapeutic use of a product for a perceived reward, including 'getting high'/euphoria (for an overview, see [76]). Since the focus here was on misuse; abuse and diversion issues, the Preferred terms (PT) for the present analysis were selected from the standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) 'Drug abuse, dependence and withdrawal' [77]; these included: 'Drug abuse', 'Substance abuse', 'Intentional product misuse', 'Dependence', 'Drug withdrawal syndrome', 'Withdrawal', and 'Withdrawal syndrome'. PTs possibly suggesting an abuse event (e.g. 'Intentional product use issue', 'Overdose', and 'Prescription drug used without a prescription') were also examined here.

Data analysis

A descriptive analysis of the characteristics of AE reports, including sociodemographic data, country of origin, and concomitant licit/illicit substances was here performed. IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, USA) was used for all descriptive analyses. Pharmacovigilance reporting measures, including reporting odds ratio (ROR); proportional reporting ratio (PRR); information component (IC); and Bayesian empirical geometric mean (EBGM), were calculated for each dataset, using the R package PhViD [78]. All four pharmacovigilance measures were computed due to differences in their sensitivity and early detection potential assess disproportionality, i.e., whether a drug-AE pair occurs more often than expected as defined by the false discovery rate (FDR), based on a 2 x 2 contingency table (Table 5) [79,80]. To identify signals above thresholds, the use of FDR, with an FDR<0.05 to indicate significance, was here used [81,82].

Table 5. Disproportionality computation of drug-Adverse Event (AE) pairs.

	# Reports with AE of interest	# Reports without AE of interest
# Reports with drug of interest	A	b
# Reports without drug of interest	C	d

Calculations for the frequentist measures, ROR [83] and PRR [84], are as follows:

$ROR = \frac{a \times d}{b \times c}$, where the ROR describes the odds of the AE of interest among specific drug reports compared to the odds of the AE of interest among all other drug reports; a large ROR suggests that the drug-AE pair is reported more often, i.e., disproportionately, than expected.

$PRR = \frac{a/(a+b)}{c/(c+d)}$, which can be interpreted as the proportion of reports with the AE of interest among specific drug reports compared to the proportion of reports with the AE of interest among all other drugs; a large PRR suggests that the drug-AE pair is reported more often than expected.

The IC [85] and EBGM [86] are Bayesian measures with more complex computations described in detail elsewhere. If the lower endpoint of the 95% credible interval for the IC (i.e., IC025) is greater than zero (i.e., positive) then it suggests that the drug-AE pair occurs in the data more often than expected. Similarly, if the lower bound of the 90% credible interval of the EBGM (i.e., EB05) is large, this suggests that the drug-AE pair occurs in the data disproportionately.

5. Conclusions

Current findings, indicating a possible semaglutide misuse/abuse issue, will need to be confirmed by further empirical investigations. These will help in better elucidating: the GLP-1R agonists' central pharmacodynamics, e.g. their interaction with a different range of receptors; the levels of availability of GLP-1R agonists for acquisition from rogue websites; and, with the help of properly designed epidemiological studies, the characteristics of their possible misuse/abuse in both the general and vulnerable populations.

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Conflicts of Interest: FS was a member of the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and is currently a member of the EMA Advisory Board (Psychiatry). JMC is a member of the ACMD's Novel Psychoactive Substances and Technical Committees. G.M. has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati. AG, SC, RVS, DRH: declare no conflict of interest.

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