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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 here evaluated 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 antidiabetics, 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 our best, this is the first study documenting the misusing/abusing potential of semaglutide in comparison with other novel antidiabetics 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

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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 glucagon-like peptide-1 receptor agonists (GLP-1 RA) semaglutide and tirzepatide, acting on both GIP and GLP-1 receptors, are now approaching the success seen with bariatric surgery [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; or the two GLP-1 analogues dulaglutide and semaglutide [6,9–14].

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 [10,15]. 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 [16]. With these medications, a range of gastrointestinal adverse effects have been reported, e.g. nausea and diarrhoea [17]; conversely, severe hypoglycaemia, fatal adverse events, acute pancreatitis, cholelithiasis, and cholecystitis are considered as rare events [1,8].

*Is there an antidiabetics' 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), metformin; lorcaserine, sibutramine, and rimonabant, which was lately dismissed from the market for severe human health risks [18]. Because of their misusing potential, some of these molecules are classified as controlled substances [18,19]. Indeed, metformin has been associated with levels of both diversion [20] and abuse [21], having been ingested either at high dosages [22], or by eating-disorder individuals [23].

A large range of newspapers' [24] reports commented about the possible existence of some novel antidiabetics' 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 [25]. Social media platforms' semaglutide promotion as a weight-loss treatment [26], and the associated increase in demand, may well have contributed to an ongoing worldwide shortage of the drug [27,28]. 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 [29,30].

In contrast with the above, it is of interest that by the time of drafting of this paper no literature reports focussing on 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 the following molecules: albiglutide; dulaglutide; exenatide; liraglutide; lixisenatide; tirzepatide; and 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 analytic timeframe an increase in the number

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of reported AER compared to remaining antidiabetics was here observed (Figure 1); overall, most reports came from the USA.

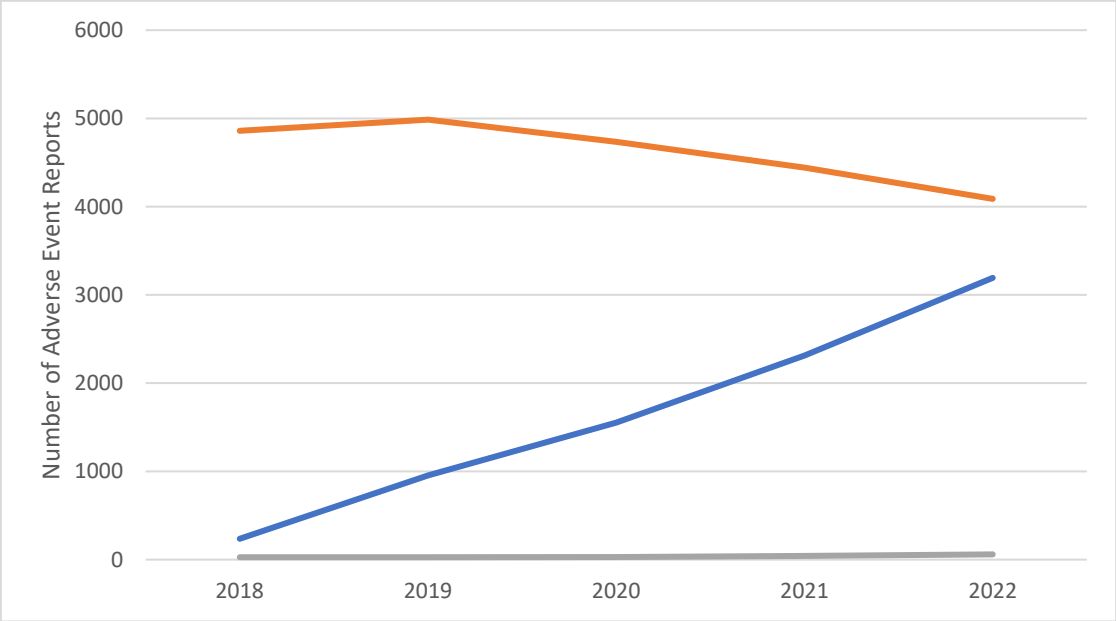


**Figure 1.** Number of Adverse Event Reports (AER) involving semaglutide, phentermine-topiramate, and other antidiabetics (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide). Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022) (semaglutide: blue colour; phentermine-topiramate; grey; remaining antidiabetics: orange).

Most of the AER 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 1).

**Table 1.** Most typically reported semaglutide; phentermine-topiramate and other antidiabetic-related Adverse Event Reports (AER). Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

| **SEMAGLUTIDE** | | **PHENTERMINE-TOPIRAMATE** | | **OTHER GLP-1-RA*** | |
|---|---|---|---|---|---|
| **Preferred Term** | **# AER** | **Preferred Term** | **# AER** | **Preferred Term** | **# AER** |
| Nausea | 1,047 | Dizziness | 15 | Nausea | 1,843 |
| Vomiting | 921 | Nephrolithiasis | 14 | Blood glucose increased | 1,604 |
| Diarrhoea | 699 | Headache | 11 | Vomiting | 1,586 |
| Pancreatitis | 492 | Weight increased | 10 | Pancreatitis | 1,459 |
| Off label use | 483 | Angle closure glaucoma | 9 | Diarrhoea | 1,426 |
| Weight decreased | 465 | Vision blurred | 9 | Acute kidney injury | 1,112 |
| Blood glucose increased | 424 | Suicidal ideation | 8 | Weight decreased | 1,082 |

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| | | | | | |
|---|---|---|---|---|---|
| Decreased appetite | 387 | Chronic kidney disease | 7 | Fatigue | 794 |
| Fatigue | 357 | Hypoesthesia | 7 | Decreased appetite | 711 |
| Dehydration | 352 | Paraesthesia | 6 | Chronic kidney disease | 689 |

*Abbreviations:* AER: Adverse Event Report; GLP-1-RA: glucagon-like peptide-1 receptor agonists. *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 AERs, whilst this event occurred with the remaining molecules in 1,705/23,110 (7.4%) of AERs (Table 2).

**Table 2.** Most typically reported semaglutide; phentermine-topiramate and other antidiabetic-related outcomes. Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

| **Semaglutide** | | **Phentermine-topiramate** | | **Other GLP-1-RA*** | |
|---|---|---|---|---|---|
| **Outcome** | **# AER** | **Outcome** | **# AER** | **Outcome** | **# AER** |
| Other outcomes | 5418 | Other outcomes | 154 | Other outcomes | 14206 |
| Hospitalized | 3479 | Hospitalized | 46 | Hospitalized | 10287 |
| Life threatening | 306 | Disabled | 14 | **Died** | **1705** |
| Disabled | 299 | Life threatening | 3 | Life threatening | 1103 |
| **Died** | **273** | **Died** | 1 | Disabled | 671 |
| Required intervention | 67 | Required intervention | 1 | Required intervention | 76 |

*Abbreviations:* AER: Adverse Event Report; GLP-1-RA: glucagon-like peptide-1 receptor agonists. *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 remaining antidiabetics selected (Ta-ble 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 'in-tentional product use issue' was reported almost 2 times as frequently (PRR= 1.80; FDR<0.01) (Table 3). Conversely, no significant differences in terms of the selected AER occurrence were here identified when comparing semaglutide vs the phentermine-topiramate combination.

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**Table 3.** Signal scores regarding drug misuse; abuse; and withdrawal-related AER for: semaglutide; other antidiabetic drugs; and phentermine-topiramate combination. Data source: Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; 2018-2022).

| | SEMAGLUTIDE VS. OTHER GLP-1-RA | | | | SEMAGLUTIDE VS. PHENTERMINE-TOPIRAMATE | | | |
|---|---|---|---|---|---|---|---|---|
| **PT (MedDRA)** | PRR | ROR | IC025 | EB05 | PRR | ROR | IC025 | EB05 |
| **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-RA: glucagon-like peptide-1 receptor agonists; IC: information component; 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 novel antidiabetics and the phentermine-

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topiramate combination. The comparison was here carried out with the help of a range of worldwide, valuable [31,32], pharmacovigilance data, as those derived from the FAERS. AERs related to semaglutide showed here steady and progressive increasing levels during the years 2018-2022; conversely, the phentermine-topiramate related AERs remained roughly stable, and AERs related to the remaining GLP-1 mimetics appeared to have decreased during the same years. Consistent with this, in the years previous to the outlined timeframe (i.e. 2018-2022) considered here, prescriptions for all antidiabetics increased, but this was especially true for those relating to semaglutide [33–36].

As expected, for both semaglutide and the other antidiabetics the most reported AER involved the gastrointestinal adverse events [37]. Conversely, the phentermine-topiramate AER most typically involved here dizziness, headache, blurred vision, hypoesthesia, and paraesthesia, which have all been reported for topiramate [38]. 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 [39,40], the molecule is considered to possess an overall favourable risk/benefit profile for patients with T2DM [41]. It may be a reason of concern, however, that an off-label prescription issue for semaglutide, but not for the remaining novel antidiabetics, 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 [16,24,27–28].

*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 [42] 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 [43]. Other extreme slimming misusing agents have included: β-2 agonists such as clenbuterol [44]; diuretics [45]; and dinitrophenol/DNP [46]. Overall, these agents are being misused and abused by vulnerable; non-obese; body dysmorphic; subjects for their image- enhancing [47], 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 obesiologists for weight loss purposes [18]. Whilst phentermine has not been previously associated with evidence of physical dependence or addiction [48], it may well possess a potential of misuse [49]. 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.

*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 [2,50], and hence with the significant weight loss, associated with the GLP-1RA semaglutide. In the central nervous system (CNS), GLP-1Rs are expressed in several brain regions involved in the regulation of metabolism and energy balance [51]. The reward-related brain regions that regulate appetitive and consumption behaviours include the mesolimbic regions' nucleus accumbens (NAc), ventral tegmental area (VTA) and amygdala [52,53], with GLP-1Rs being located in the mesolimbic system [54,55]. Furthermore, the gut–brain axis peptide ghrelin enhances dopamine release in the VTA [56]. 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 [57]. In line with this, a recent randomized-controlled trial showed that 1 year after having withdrawn a weekly semaglutide 2.4 mg treatment,

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participants regained two-thirds of their weight loss [58]. Indeed, GLP-1 analogues may reduce the rewarding effects of palatable food intake (for a review, see also [56]) and the food-related brain responses in both T2DM and obese subjects in insula, amygdala, putamen, and orbitofrontal cortex [59]. Consistent with this, GLP-1R agonists can reduce: cue- and drug-induced fentanyl seeking [60]; physical and behavioural effects of morphine withdrawal [55]; cue-, stress-, and drug-induced heroin-seeking [61]; use of cocaine, amphetamine, alcohol, and nicotine in animals when administered over several days or weeks [61–64]. 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 [65]. Another study demonstrated that weekly exenatide significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients [66]. Therefore, GLP-1 RA are gaining increasing attention as new therapeutic agents for the treatment of reward system-related disorders [54].

*The potential use of GLP-1 Ras 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) [67], Alzheimer Disease (AD), diabetes, and strokes [68]. Consistently, exenatide administered weekly had positive effects on practically defined off-medication motor scores in Parkinson's disease, and this outcome was sustained beyond the period of exposure [69]. Interestingly, the GLP-1 RA exenatide in its extended-release formulation has been successfully employed to alleviate the motor symptoms of PD patients [70], 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 [68,71], 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

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Dashboard [72]. 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 [73]). 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' [74]; 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, most common diagnoses, routes of administration 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 [75]. All four pharmacovigilance measures were computed due to differences in their sensitivity and early detection potential [76,77]. To identify signals above thresholds, the use of false discovery rate (FDR), with an FDR<0.05 to indicate significance, was here used [78,79].

## 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 GLP1-R 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.

**Author Contributions:** Conceptualization, F.S., S.C., and D.P.; methodology, F.S., S.C. and R.V.-S.; formal analysis and data management, R.V.-S.; writing—original draft preparation, F.S., S.C., D.P.; writing, reviewing and editing, S.C., J.M.C., G.M., A.G. and D.P.; supervision, G.M.; S.L.S.; F.S. All authors have read and agreed to the published version of the manuscript.

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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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**Websites apparently offering novel diabetes medicines for sale; no prescription was required (search carried out on 9 March 2023 and on 6 May 2023)**

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