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Suicidal Ideation and Glucagon-like Peptide-1 Receptor Agonists: An Examination of Real-Word Data Gathered from the European Pharmacovigilance Database

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Abstract:

Context: It has just now come to light that liraglutide and semaglutide medications may carry the risk of suicide. So, we set out to study the likelihood of reporting suicidal thoughts and actions among GLP-1 receptor agonists. Methods: The European Pharmacovigilance database was the subject of a retrospective pharmacovigilance investigation covering the years 2018–2023. It was determined if GLP-1 RAs were more likely to report suicidal thoughts or behaviors by using disproportionality analysis (reporting odds ratio, ROR). Findings: 230 reports of incidents involving suicide thoughts or behavior were recorded. The following GLP-1 RAs were most often reported: liraglutide (38.3%), semaglutide (36.5%), and dulaglutide (16.1%). Suicidal thoughts (65.3%) and attempts (19.5%) were the most often reported occurrences. When comparing semaglutide to dulaglutide and exenatide, the disproportionality analysis revealed that semaglutide had a greater reporting likelihood of suicidal occurrences (ROR, 2.05; 95%CI, 1.40-3.01 vs. 1.81; 1.08-3.05). Similarly, compared to dulaglutide (ROR, 3.98; 95%CI, 2.73-5.82) and exenatide (ROR, 3.52; 95%CI, 2.10-5.92), liraglutide was linked to a greater reporting likelihood of suicide occurrences. While liraglutide had a higher reporting probability, semaglutide had a lower one (ROR, 0.51; 95%CI, 0.38-0.69). Results: Compared to other GLP1 RAs, semaglutide and liraglutide had much greater reporting probabilities of suicidal episodes. While the research does provide the reporting rates of suicide-related occurrences with GLP-1 RAs, it does not demonstrate causation. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency will likely address this matter in the future.

Relevant terms: disproportional reporting, glucagon-like peptide-1 receptor agonists, safety, pharmacovigilance, and a retrospective analysis.

1. Introduction

The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has been conducting a continuing safety review of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) since 11 July 2023 [1]. The risk of suicidal and self-harming thoughts in patients treated with these medicines is the primary focus of the data evaluation. It is common practice to provide GLP-1 RAs, which are incretin-mimetic drugs, to patients with type 2 diabetes mellitus (T2DM) [2]. This family of medications may reduce blood sugar levels, inhibit glucagon release in either hyperglycemia or euglycemia, and raise insulin secretion in response to hyperglycemia by activating GLP-1 receptors. Six GLP-1 RAs have been approved thus far in Europe. In 2006, exenatide was approved for the treatment of type 2 diabetes. In the years that followed, the European Medicines Agency green-lit liraglutide in 2009, lixisenatide in 2013, dulaglutide in 2014, and semaglutide in 2018. For financial reasons, the holder of the marketing authorization requested in 2018 that another GLP-1 RA, albiglutide, be removed from sale in Europe. It is standard practice to inject GLP-1 RAs under the skin. One pharmaceutical breakthrough that aims to increase compliance in diabetic patients is the new oral semaglutide formulation that will be launched in 2020. Patients at high risk for cardiovascular consequences from diabetes mellitus, such as those with coronary syndromes, heart failure, or chronic renal disease, have shown improvement in their condition after using GLP-1 RAs, which is a step forward in the field of pharmacology [3]. At the beginning of therapy and during dosage escalation, gastrointestinal symptoms (nausea, vomiting, diarrhea) are the most prevalent side effects of GLP-1 RAs. Thus, a slow up-titration is necessary to lessen the severity of gastrointestinal side effects [3]. Delays in stomach emptying, decreased food intake, and weight loss are some of the additional effects of GLP-1 RAs that have been shown over the course of many decades of study, in addition to their hypoglycemic, endocrine, and cardiovascular effects [4]. Reason being, GLP-1 receptors are expressed throughout the CNS, which includes

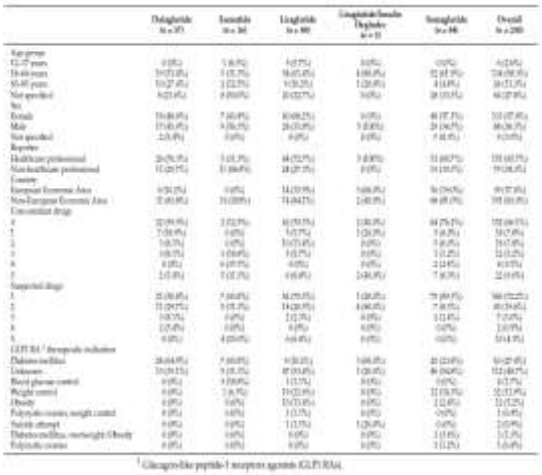
the region of the brain responsible for controlling hunger [5]. This is why GLP-1 RAs work by making you feel fuller for longer and less hungry. Because of these extra features, they are more popular for controlling body weight. For the treatment of obesity or overweight, two GLP-1 RAs—liraglutide (2015) and semaglutide (2022)—were approved, respectively. In particular, SaxendaR (liraglutide) andWegovyR (semaglutide) were approved as adjuncts to a reduced-calorie diet and increased physical activity for weight management in adults with a body mass index (BMI) of ≥30 kg/m2 (obesity) or ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity (e.g., prediabetes, type 2 diabetes mellitus, hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease) and as an adjunct to healthy nutrition and increased physical activity for weight management in obese adolescents (≥12 years) with a BMI corresponding to 30 kg/m2 for adults or with body weight above 60 kg.

2. Results

2.1. Features of Case Safety Reports for Individuals

There were 41,236 GLP-1 RA-related ICSRs recovered from EV between January 1, 2018, and July 10, 2023. Of these, 230 (or 0.6% of the total) reported at least one suicide attempt. In Table 1 you can see the detailed information about every GLP1 RA. Among the GLP1 RAs, liraglutide topped the list with 88 reports (38.3%), followed by semaglutide with 84 reports (36.5%), dulaglutide with 37 reports (16.1%), exenatide with 16 reports (6.9%), and liraglutide/insulin degludec with 5 reports (2.2%). The oral formulation of semaglutide (RybelsusR) was associated with 9 ICSRs (10.7%), whereas the approved formulation for weight management (WegovyR) was associated with 11 ICSRs (13.1%). In contrast, 60 ICSRs (68.2% of the total) with liragluride were associated with the approved weight control formulation (SaxendaR). In EV, there was no reported ICSR of suicide with lixisenatide. Given that an ICSR might include more than one suspected medication, we discovered that ICSRs involving suicide reported one GLP-1 RA. The age range of 18-64 years accounted for 134 (58.3%) of the ICSRs recorded, with 133 (57.8%) being female. Healthcare professionals were the most common reporters (n = 151; 65.7%), while ICSRs originated mostly from regions outside of the European Economic Area (n = 191; 83.0%). Most ICSRs did not specify a therapeutic indication (n = 112; 48.7%), but those that did were for the management of obesity or weight (n = 48; 20.9%) or diabetes or blood glucose (n = 67; 29.1%). In particular, 63 people (27.4% of the total) indicated diabetes mellitus as an indication, whereas 32 people (13.9%) reported weight control. With the exception of exenatide, the majority of ICSRs reported success in controlling diabetes or blood glucose levels with dulaglutide (n = 24) and semaglutide (n = 20). In contrast, liraglutide and semaglutide were associated with success in controlling obesity or weight (n = 30 and n = 14, respectively). There were 166 ICSRs (72.2% of the total) when the GLP1 RA was the only suspected drug, and 152 (66.1% of the total) where no concurrent medicine was recorded.

Table 1. Demographic characteristics of Individual Case Safety Reports (ICSRs) reporting suicide events associated with suspected drugs: dulaglutide, exenatide, liraglutide, liraglutide/insulin degludec, or semaglutide; sorted by age, sex, reporter type, country of origin, and number of drugs.



2.2. Descriptive Characteristics of Suicidal Events

Out of 230 ICSRs, 236 were determined to be suicide attempts (Table 2). There were 154 reports of suicidal thoughts (65.3% of the total) and 46 reports of suicide attempts (19.5% of the total). The most common reports of suicidal thoughts and attempts were with liraglutide (16 out of 90; 17.8%) and semaglutide (67 out of 86; 77.9%), respectively, whereas the most common reports of suicidal ideation and attempts were with dulaglutide (15 out of 38; 39.5%) and liraglutide. The majority of the reported incidents involved females (99 out of 137, or 72.3%, of the total), while neither incident included men (22 out of 137, or 16.1%; see Table 2). With the exception of one unidentified occurrence, all suicide attempts were considered very severe. "Other medically important condition" was the most often cited reason for the severity of the incidents (n = 161; 68.2%). Out of 106 ICSRs (44.9%), the result was unavailable; nonetheless, 31.4% of those cases were resolved. In fourteen ICSRs (4.9%), the result was lethal. Table 3 contains all the criteria for severity and outcome for each GLP1 RA.

Table 2 shows the distribution of suicide occurrences for the following types of semaglutide: dulaglutide, exenatide, liraglutide, liraglutide/insulin degludec, and sex.

	Dulaglutide (n = 38)	Exenatide (n = 17)	Liraglutide (n = 90)	Liraglutide/Insulin Degludec (n = 9)	Semaglutide (n = 86)	Overall (n = 236)	Female (n = 137)	Male (n = 99)	Not Specified (n = 0)
Events									
Completed suicide	2 (5.3%)	1 (5.9%)	5 (5.6%)	0 (0%)	3 (3.5%)	11 (4.7%)	2 (1.5%)	9 (9.1%)	0 (0%)
Depression suicidal	2 (5.3%)	1 (5.9%)	5 (5.6%)	0 (0%)	9 (10.5%)	17 (7.2%)	11 (8.0%)	6 (6.1%)	0 (0%)
Suicidal behaviour	2 (5.3%)	2 (11.8%)	1 (1.1%)	0 (0%)	0 (0%)	5 (2.1%)	2 (1.5%)	3 (3.1%)	0 (0%)
Suicidal ideation	17 (44.7%)	10 (58.8%)	60 (66.7%)	0 (0%)	67 (77.9%)	154 (65.3%)	99 (72.3%)	67 (67.7%)	8 (88.9%)
Suicide attempt	15 (39.5%)	3 (17.6%)	16 (17.8%)	5 (100%)	7 (8.1%)	46 (19.5%)	22 (16.1%)	23 (25.0%)	1 (11.1%)
Suspected suicide	0 (0%)	0 (0%)	3 (3.3%)	0 (0%)	0 (0%)	3 (1.3%)	1 (0.7%)	2 (2.2%)	0 (0%)

Table 3. Seriousness and outcome criteria of suicidal events reported with dulaglutide, exenatide,

liraglutide, liraglutide/insulin degludec, and semaglutide.

	Dulaglutide (n = 38)	Exenatide (n = 17)	Liraglutide (n = 90)	Liraglutide/Insulin Degludec (n = 9)	Semaglutide (n = 86)	Overall (n = 236)
Seriousness Criteria						
Caused/prolonged hospitalization	10 (26.3%)	5 (29.4%)	10 (11.1%)	4 (80.0%)	6 (8.3%)	37 (15.7%)
Life-threatening	3 (7.9%)	4 (23.5%)	6 (6.7%)	1 (20.0%)	6 (7.0%)	20 (8.5%)
Other medically important condition	23 (60.5%)	7 (41.2%)	65 (70.8%)	0 (0%)	66 (79.1%)	161 (68.2%)
Results in death	2 (5.3%)	1 (5.9%)	8 (8.9%)	0 (0%)	3 (3.5%)	14 (5.9%)
Not reported	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	1 (0.4%)
Disabling	0 (0%)	0 (0%)	2 (2.2%)	0 (0%)	1 (1.2%)	3 (1.3%)
Outcome						
Fatal	2 (5.3%)	1 (5.9%)	8 (8.9%)	0 (0%)	3 (3.5%)	14 (5.9%)
Not Recovered / not resolved	3 (7.9%)	1 (5.9%)	9 (10.0%)	0 (0%)	13 (15.1%)	24 (10.2%)
Recovered / resolved	11 (28.9%)	2 (11.8%)	26 (28.9%)	2 (40.0%)	33 (38.4%)	74 (31.4%)
Recovering / resolving	3 (7.9%)	0 (0%)	8 (8.9%)	0 (0%)	6 (7.0%)	17 (7.2%)
Unknown	21 (55.3%)	13 (76.5%)	39 (43.3%)	3 (60.0%)	30 (34.9%)	106 (44.9%)
Recovered / resolved with sequelae	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.2%)	1 (0.4%)

2.3. Disproportionality Analysis

When compared to other GLP1 RAs, semaglutide and liraglutide showed statistically significant differences in the disproportionality analysis. A higher risk of reporting suicidal thoughts or actions was associated with semaglutide compared to dulaglutide (ROR, 2.05; 95%CI, 1.40-3.01) or exenatide (ROR, 1.81; 95%CI, 1.08-3.05) and liraglutide (ROR, 3.98; 95%CI, 2.73-5.82) or exenatide (ROR, 3.52; 95%CI, 2.10-5.92). Alternatively, compared to ligaltudide, semaglutide had a reduced reporting probability (ROR, 0.51; 95%CI, 0.38-0.69). Figure 1 shows that no other comparisons showed statistically significant differences.

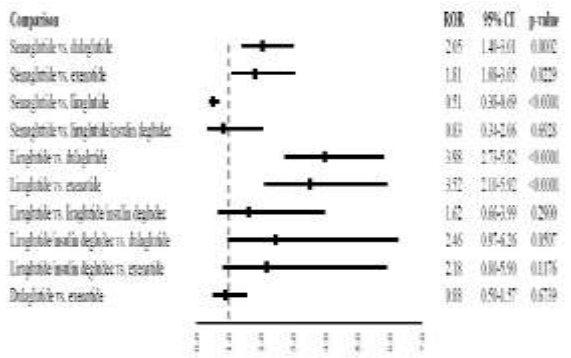


Figure 1. Reporting probabilities of suicidal events among GLP-1 receptor agonist. Data are expressed as reporting odds ratios (RORs) and their 95% confidence intervals (95%CI).

3. Discussion

This is the first pharmacovigilance research to use the European pharmacovigilance database to assess the reporting of suicide episodes as suspected adverse medication reactions related with GLP1 RAs. The risk management strategies for these medications in Europe did include a discussion of GLP1 RA-induced suicide attempts. The Icelandic Medicines Agency was made aware of them after reports of suicidal ideation and self-harm involving liraglutide and semaglutide were received [1]. The research results show how often GLP-1 RAs are reported in relation to suicide attempts. Still, the PRAC will give a verdict after additional examination into the cause and effect. When comparing semaglutide to exenatide and dulaglutide, we discovered that the reporting of suicidal occurrences was two times higher with the former. There was a 4-fold increase in the reporting of suicide occurrences with liraglutide compared to exenatide and a 3.5-fold increase with dulaglutide, respectively, raising this estimate even higher. Additionally, semaglutide shown a decreased reporting of suicidal occurrences as compared to liraglutide. One possible explanation for this result and the decreased reporting of suicide incidents is the recent marketing authorization of semaglutide. In addition to treating diabetes mellitus, both medications are used to treat obesity and overweight [13,14]. Their main impact is to decrease hunger. Concerns about neuropsychiatric side effects are common among centrally acting anti-obesity medications [15,16]. The liraglutide weight management clinical trials program's pooled post hoc analysis of neuropsychiatric safety data on liraglutide 3.0 mg indicated that both the liraglutide and placebo groups had low incidences of depression, anxiety, and insomnia (≤4%), with a slight increase in insomnia and suicidal ideation for liraglutide [17]. Research on type 2 diabetes using lower dosages of liraglutide (up to 1.8 mg) has not shown any evidence of neuropsychiatric side effects in clinical studies [18,19]. Consequently, it seems that the increased risk of suicide associated with GLP1 RAs may be linked to the usage of greater dosages for the purpose of weight control. Patients using liraglutide 3.0 mg should be closely observed for signs of depression or suicidal thoughts; if these symptoms occur, the medicine should be stopped immediately, according to the US prescription guidelines [20]. Semaglutide for obesity (WegovyR) is used at larger doses for weight management than type 2 diabetes, and the US prescription label for this medication has the same warning [21]. Nevertheless, none of the GLP-1 RAs included in the European SmPCs mention these cautions.

Because of the correlation between suicidal thoughts and actions and hypothalamic-pituitary-adrenal axis hyperactivity, the hypothalamic-pituitary-adrenal axis action may be a contributing factor to the increased risk of suicide occurrences while using GLP-1 RAs [5]. The function of GLP1 in the neurological system remains unclear, however, according to the available data. In addition to its effects on neuroinflammation and neurotransmitter balance, GLP1 has been shown to protect neurons and glia against oxidative stress [23]. Furthermore, recent research aimed at regulating energy balance have focused on the possible connection between GLP-1 and serotonin pathways [24,25]. Potentially contributing to the etiology of depression and thoughts of suicide, this relationship cannot be ruled out. This further complicates any attempt to draw a causal inference. Suicidal thoughts and actions may develop in GLP1 RA patients for a variety of reasons, some of which are medical and others of which are social. 4. Ingredients and Procedures

4.1. Research Plan

This research compared the reporting likelihood of suicidal episodes amongst GLP1 RAs as part of a retrospective European pharmacovigilance analysis.

4.2. Research Material

The EMA's European pharmacovigilance database, or EV, is where any adverse events that, in the view of the reports, may be associated with the administration of a medicine or vaccine are recorded and analyzed. As a result, it compiles all reports of adverse drug reactions (ADRs) or adverse events after vaccinations (AEFIs) that have been reported to medicines regulatory agencies by individuals or healthcare providers [28]. Continuous medication monitoring includes pharmacovigilance database analysis, which permits the extrapolation of safety data and signals from the actual world [48,49]. The data gathered by the EV is made publicly accessible on the EMA website (www.adrreports.eu, accessed on 13 July 2023) in accordance with a transparency policy.

4.3. Retrieving Data

We gathered all ICSRs that reported at least one GLP-1 RA as a suspected medication from 1 January 2018 (the EMA authorization year of the most current GLP-1 RA semaglutide) to 10 July 2023 and uploaded them to the EMA website (www.adrreports.eu) on 13 July 2023. Using the Anatomical Therapeutic Chemical (ATC) Classification A10BJ, which encompasses semaglutide, liraglutide, exenatide, lixisenatide, dulaglutide, albiglutide, and beinaglutide, we were able to identify all GLP1 RAs. Albiglutide was really taken off the European market for commercial reasons [50], and beinaglutide is only allowed in the US [51] and China [52], therefore we didn't include it in our study. We have made sure to add the insulin degludec/liraglutide combo medication.

5. Conclusions

A total of 230 ICSRs involving GLP1 RAs and suicide attempts were identified in our investigation. When compared to other GLP1 RAs, semaglutide and liraglutide had the highest reporting probability, making them the most reported medicines. The approved formulation for weight control accounted for 13.1% of semaglutide ICSRs and 68.2% of liraglutide ICSRs. Suicidal thoughts and attempts in women and actual suicide in men were the most often reported occurrences. In light of the fact that the clinical trials lacked the ability to assess neuropsychiatric events in particular, more research is required to account for all prospective suicide risk variables. This study highlights the need of prescription GLP1 RAs in a way that rigorously follows evidence-based guidelines. Additionally, it emphasizes the need to enhance pharmacovigilance efforts in order to make more data on GLP-1 RAs available in the future.

References

1. European Medicine Agency. EMA Statement on Ongoing Review of GLP-1 Receptor Agonists. Available online: https://www. ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists (accessed on 31 July 2023).

2. Górriz, J.L.; Romera, I.; Cobo, A.; O'Brien, P.D.; Merino-Torres, J.F. Glucagon-like Peptide-1 Receptor Agonist Use in People Living with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Narrative Review of the Key Evidence with Practical Considerations. Diabetes Ther. 2022, 13, 389–421. [CrossRef] [PubMed]

3. Davies, M.J.; Aroda, V.R.; Collins, B.S.; Gabbay, R.A.; Green, J.; Maruthur, N.M.; Rosas, S.E.; Del Prato, S.; Mathieu, C. Management of Hyperglycaemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022, 45, 2753–2786. [CrossRef] [PubMed]

4. Nauck, M.A.; Quast, D.R.;Wefers, J.; Meier, J.J. GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes—State-of-the-Art. Mol. Metab. 2021, 46, 101102. [CrossRef] [PubMed]

5. Drucker, D.J. GLP-1 Physiology Informs the Pharmacotherapy of Obesity. Mol. Metab. 2022, 57, 101351. [CrossRef]

6. Chiappini, S.; Vickers-Smith, R.; Harris, D.; Pelletier, G.D.P.; Corkery, J.M.; Guirguis, A.; Martinotti, G.; Sensi, S.L.; Schifano, F. Is There a Risk for Semaglutide Misuse? Focus on the Food and Drug Administration's FDA Adverse Events Reporting System (FAERS) Pharmacovigilance Dataset. Pharmaceuticals 2023, 16, 994. [CrossRef]

7. Ozempic: French Authorities. Issue Alert for Anti-Diabetic Drug Misused for Weight Loss. Available online: https: //www.lemonde.fr/en/health/article/2023/03/02/ozempic-french-authorities-issue-alert-for-anti-diabetic-drug-misusedfor- weight-loss_6017913_14.html (accessed on 1 August 2023).

8. Italian Medicines Agency. Direct Healthcare Professional Communications Regarding OzempicR (Semaglutide). 2023. Available online: https://aifa.gov.it/-/nota-informativa-importante-su-ozempic%C2%AE-semaglutide- (accessed on 1 January 2024).