ACTA Scientific Neurology (ISSN: 2582-1121)

Volume 7 Issue 5 May 2024

Case Report

Hemiplegic Migraines Exacerbated using an Injectable GLP-1 Agonist for Weight Loss

Edward J Modestino[1]*, Abdalla Bowirrat[2], Kai-Uwe Lewandrowski[3,4], Alireza Sharafshah[5], Rajendra D Badgaiyan[6], Panayotis K Thanos[7], David Baron[8], Catherine A Dennen[9], Igor Elman[10], Keerthy Sunder[11], Kevin T Murphy[12] and Kenneth Blum[2,4,8,12,13]

[1]Department of Psychology, Curry College, Milton, MA, USA

[2]Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel

[3]Department of Orthopaedics, Fundación Universitaria Sanitas, Bogotá, DC, Colombia

[4]Division of Personalized Pain Therapy and Education, Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA

[5]Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[6]Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA

[7]Behavioral Neuropharmacology and Neuroimaging Laboratory, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, Clinical Research Institute on Addictions, University at Buffalo, Buffalo, NY, USA

[8]Center for Sports, Exercise, Global Mental Health, Western University Health Sciences, Pomona, CA, USA

[9]Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA

[10]Department of Psychiatry, Harvard University School of Medicine, Cambridge, MA., USA

[11]Department of Medicine, University of California, Riverside School of Medicine, Riverside, CA, USA

[12]Karma Doctors & Karma TMS, and Suder Foundation, Palm Springs, CA, USA

[13]Division of Personalized Neuromodulation, PeakLogic, LLC., Del MAR, CA., USA

***Corresponding Author:** Edward J Modestino, Department of Psychology, Curry College, Milton, MA, USA.

DOI: 10.31080/ASNE.2024.07.0731

Received: February 22, 2024

Published: April 19, 2024

Abstract

The widespread adoption of Glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of obesity and diabetes has raised concerns about their potential adverse effects, including the induction of depression and suicide ideation. We report on a male patient in his early 50s with a complex medical history, including adult Attention-Deficit/Hyperactive Disorder, narcolepsy with cataplexy, and major depressive disorder in remission, who experienced exacerbated hemiplegic migraines after initiating treatment with an injectable GLP-1 agonist (Saxenda) for weight loss. Despite a previous history of experiencing hemiplegic migraines once or twice a year, the patient reported daily occurrences of migraines, many of which were hemiplegic, during the 60 days of GLP-1 agonist treatment. The migraines abated only upon discontinuation of the medication. This case underscores the need to carefully consider patient history and potential genetic predispositions when prescribing GLP-1 agonists, highlighting the complex interactions between these medications, existing comorbidities, and the dopaminergic and calcitonin gene-related peptide pathways. Our findings suggest that GLP-1 agonists, while beneficial for some, may pose significant risks for patients with specific genetic backgrounds or neurological conditions, calling for personalized approaches to treatment and increased awareness of potential adverse effects.

Keywords: Hemiplegic Migraines; Injectable GLP-1; Weight Loss; Adverse Effects

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists have become very prevalent anti-obesity/diabetes pharmaceuticals sold in the United States. This case report aimed to uncover potential adverse effects of a GLP1 agonist generalized as one of the anti-addiction compounds [1]. Our team has uncovered a mechanism by which GLp1 agonism could induce depression and suicide ideation in patients as well as other adverse effects. Specifically, we believe that using GLP-1 agonism might be therapeutically advantageous in situations of known hyperdopaminergia, but it could potentially be determinantal in patients with known or unknown hypodopaminergia, and we suggest against its use with putative long-term induction of suicidal ideation (SI). In our previous research [2], we filtered out 31 genes based on the target of GLP1R and its enzymes and carrier, as well as GeneCards best-scored genes for SI plus 10 genes of Genetic Addiction Risk Severity (GARS) test. A STRING-MODEL refined 29 completely connected genes and further primary analyses indicated associations of GLP1R with DRD3, BDNF, CREB1, CRH, IL6, and DPP4 genes. Deep in silico Enrichment analysis revealed a dopaminergic pathway and highly significant depressive phenotypes resulting from the candidate genes. Finally, we searched for the plausible negative impacts of GLP1R agonists as the addiction alternatives by primary and deep in silico analyses and introduced multiple findings supporting GLP1R agonists, which can induce depression phenotypes. This finding also revealed that GLP1R agonists overlapped with addictive behaviors, all in RDS and dopamine regulation. Consequently, GLP1R agonists might be double-edged swords activating anti-addictive results and inducing Suicide Ideation through empowering the depressive phenotypes.

In the current case report, we highlight a patient's unfortunate experience showing that hemiplegic migraines were exacerbated using an injectable GLP1 agonist for weight loss.

Case Presentation

The patient was a male in his early 50s who was born and was living in the northeastern region of the United States. The patient's history included a diagnosis of adult Attention-Deficit/Hyperactive Disorder combined type in his early 20s with lifelong symptoms, a comorbid diagnosis of narcolepsy with cataplexy, and major depressive disorder remission. These conditions were largely under control with the use of methylphenidate, clonidine, and fluoxetine.

The patient sought treatment for attacks commencing with a subjective heart palpitation that moved into the same pounding in his head, leading to headache and progressing into hemiplegic paralysis, usually on the left half of his body, migraine, aura, lasting up to 24 hours. The patient explained that these attacks occurred maybe once or twice a year. The patient had been experiencing these attacks for the last 12 years and thought they were transient ischemic attacks associated with an undiagnosed arrhythmia. Associated symptoms included trouble speaking, confusion, memory problems, and attentional problems more severe than those from his Attention-Deficit/Hyperactivity or narcolepsy. Importantly, these attacks seemed to be different from the patient's cataplexy, although both were triggered by various stressors, including arguments with his spouse and stressful situations related to his career. Based on the subjective experience with these attacks commencing with heart palpitations, he was seen by a cardiologist and given a series of tests, including a 30-day halter monitoring of his heart and an echocardiogram. Results of the heart monitor showed the patient had a single incident of non-sustained ventricular tachycardia (Figure 1). and other rare incidents of early beats. The results of the echocardiogram divulged normal heart function and normal valves. The cardiologist prescribed low-dose metoprolol, but it was discontinued within a month due to side effects.

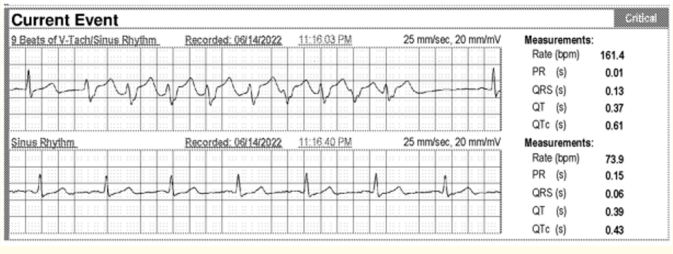


Figure 1: Incident of non-sustained ventricular tachycardia (NSVT).

Additionally, the patient was referred to a neurologist, a stroke expert, to determine the origin of these attacks. The neurologist diagnosed the patient with migraine aura without headache, non-familial hemiplegic migraine, and an impairment in balance. The neurologist prescribed Ubrelvy, an oral calcitonin gene-related peptide (CGRP) antagonist, to treat his migraines. The neurologist ordered various magnetic resonance imaging of the patient's blood vessels in the neck and head, and brain imaging (magnetic resonance angiography, and anatomical magnetic resonance imaging of the brain). Results of the magnetic resonance angiography divulged blood vessels in the neck and in the head with 0% stenosis. Brain imaging revealed moderate cerebral white matter hyperintensities

throughout the deep frontoparietal regions, mild cerebral atrophy, and mild nonspecific periventricular white matter gliosis. Figures of the MRIs are as follows (Figures 2-5). The radiologist attributed these results to be consistent with those with severe chronic migraine headaches. A neuropsychological assessment ordered by the neurologist divulged the patient still showed symptoms of Attention-Deficit/Hyperactivity Disorder, hypovigilance from sleep attacks due to narcolepsy and a visual memory impairment that was not seen in previous neuropsychological assessments.

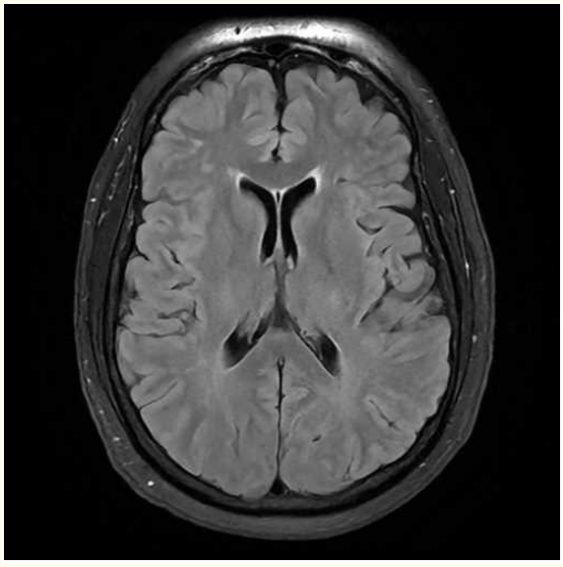


Figure 2. Axial plane FLAIR MRI of white matter hyperintensities around the ventricles.

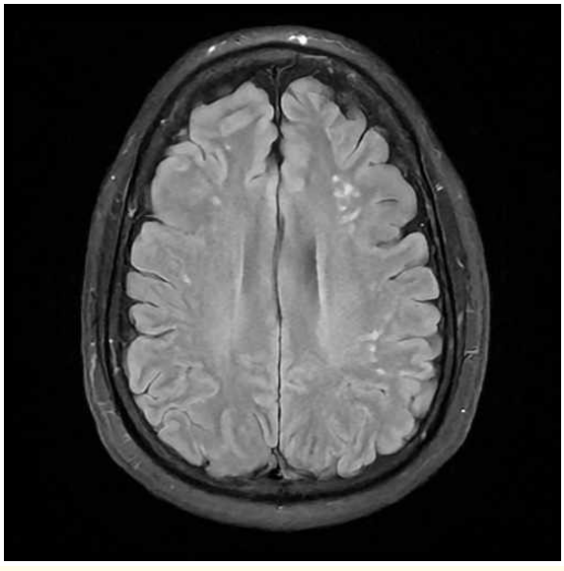


Figure 3. Axial plane FLAIR MRI of white matter hyperintensities.

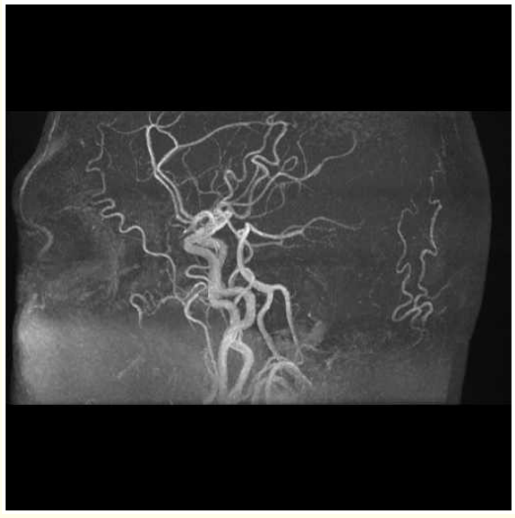


Figure 4. Brain MRA showing 0% stenosis.

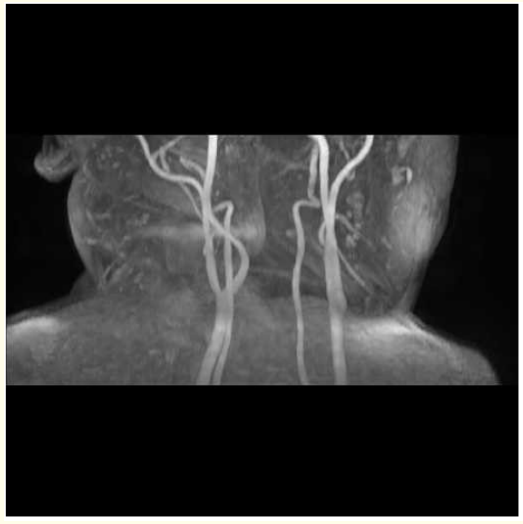


Figure 5. Neck MRA showing 0% stenosis.

As the patient assumed he had atrial fibrillation, for which his late brother (listed a one of the causes of his brother's demise on his death certificate), father, and maternal uncle all been diagnosed, and was having transient ischemic attacks as all these same relatives had as a result, the patient had undertaken a regimen of caloric restriction (1,200 kcal daily), a low fat and cholesterol diet, and an extreme exercise regimen (a half hour of cardiovascular exercise, and over an hour of weight training on various machines) several times a week, as well as sessions with a personal trainer at a local fitness center. The patient lost a total of 85 pounds over a period of two years. Unfortunately, despite maintaining this

strict diet and exercise regimen, the patient regained nearly all this weight in three years. The patient sought out endocrinologists, metabolic disorder specialists, dieticians, nutritionists, and bariatric physicians. The patient watched a documentary and learned that many people experienced this due to "metabolic adaptation". The patient was instructed by his nutritionist to stop exercising and to slowly increase his calories in the hopes of slowly increasing his resting metabolic rate. A bariatric physician confirmed the patient had a "metabolic adaptation" and initiated treatment of the unexpected weight gain with an injectable GLP-1 agonist (Saxenda) in a stepwise dosage increase, just two months after the patient received a diagnosis of hemiplegic migraines (with attacks occurring for more than a decade prior). Over the sixty days the patient took this treatment, he reported having migraines, many hemiplegics, nearly every day, which abated only with the use of Ubrelvy. As noted earlier, the patient experienced hemiplegic migraines only once or twice a year.

Thus, having these attacks nearly daily while taking Saxenda was a concern. The patient continued to take this medication as he thought the side effect of migraines would abate, but it did not. The patient discontinued the Saxenda at 60 days. Since discontinuing the Saxenda, the patient's experience of hemiplegic migraines had decreased in frequency to one every few months or less.

Adverse effects reported for glp1 agonism

While GLP-1 receptor agonists have become extremely popular over recent years, especially in the treatment and management of type 2 diabetes and obesity, we would be remiss not to discuss the adverse side effects of these medications. The long-term safety of GLP-1 receptor agonists, however, has not been established, as the majority of clinical trials are less than four years in duration. GLP-1 based therapies work by reducing the appetite and feelings of hunger, which slows the release of food from the stomach and increases feelings of fullness after eating. The most common side effects are predominantly gastrointestinal, specifically nausea, vomiting, and diarrhea [3]. These symptoms occur in 10-50% of patients, are usually mild, and occur in the first few weeks of treatment, reducing over time [4,5]. In addition, in a network meta-analysis involving 236 clinical trials, GLP-1 receptor agonists were associated with more adverse events that lead to treatment discontinuation when compared with oral agents [6].

Treatment with GLP-1 receptor agonists has also been linked to a higher risk of acute pancreatitis and biliary/gallbladder disorders, such as cholelithiasis and cholecystitis [7-12]. Treatment with GLP-1-based therapy, specifically sitagliptin and exenatide, was linked to an increased risk of hospitalization for acute pancreatitis in a study that utilized a large insurance database [13]. Sodhi et al. compared the use of GLP-1 agonists with naltrexone/bupropion and found that the evidence favors GLP-1 agonists to have a greater risk for pancreatitis, bowel obstruction, gastroparesis, and possibly biliary disease [14-16]. Additionally, case reports have indicated that exenatide users have a higher risk of pancreatic cancer, subclinical pancreatic inflammation, and neuroendocrine tumors, however no clear causal relationship has been established [12,15-17]. Additionally, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have not found sufficient evident to prove that GLP-1 receptor agonists use leads to an increased risk of pancreatic cancer [18,19].

Research has also indicated that GLP1 analogs (liraglutide and dulaglutide) have been associated with an increased incidence of benign and malignant thyroid C-cell hyperplasia and tumors in rodents [20,21], however, this may not relate to humans because humans have less C cells and the expression of GLP-1 receptors is very low when compared to rats [21]. Therefore, GLP-1 receptor agonists are currently contraindicated for patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) 2A or 2B. GLP-1 receptor agonists such as semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide have been linked to a small number of angioedema and anaphylaxis cases [22-26]. There have also been case reports of acute renal failure/renal insufficiency in patients using exenatide twice daily, though this was typically seen in the setting of severe gastrointestinal side effects causing dehydration [27-29]. Overall, acute kidney injury (AKI) has been infrequently reported with GLP-1 use [30,31]. Finally, there have been care reports of exenatide being linked to drug-induced immune thrombocytopenia, which can result in serious bleeding [32,33].

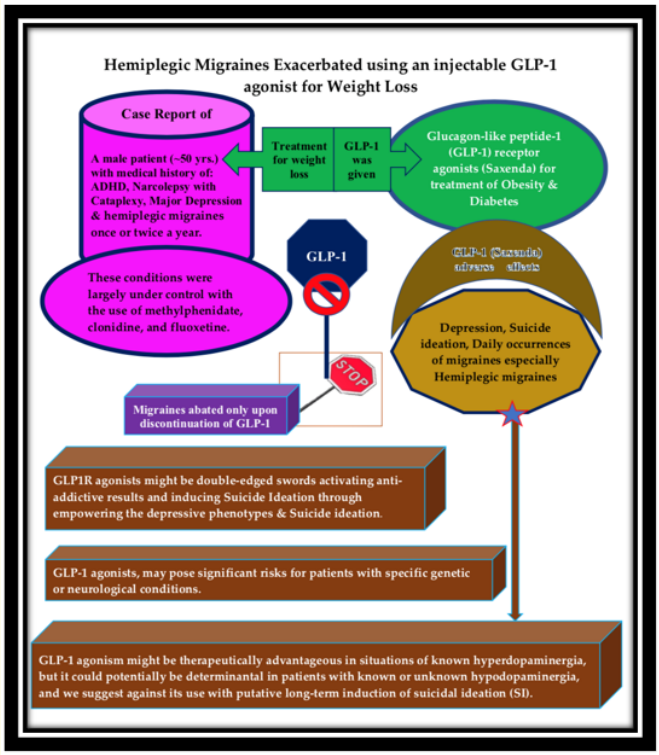
Finally, as of July 2023, the EMA has begun reviewing data regarding the risk of suicidal thoughts and thoughts of self-harm associated with GLP-1 receptor agonists, including Ozempic (semaglutide), Saxenda (liraglutide), and Wegovy (semaglutide) [34,35]. This review was prompted by the Icelandic Medicines Agency in response to reports of suicidal thoughts and self-harm among patients taking liraglutide and semaglutide medications. Authorities have retrieved and are currently reviewing approximately 150 reports of potential suicide attempts and self-harm incidents. Furthermore, from 2010-2023 the FDA has received 265 reports of suicidal thoughts in patients taking GLP-1 receptor

agonists, particularly tirzepatide, liraglutide, and semaglutide, prompting a review of these medications [34,35]. Indeed, this is not surprising in terms of our cautionary note concerning attenuation rather than promotion of enhanced dopamine signaling in the long-term, potentially leading to hypodopaminergia.

Glucoregulatory function and GLP-1 receptor agonists

In terms of the Brain Reward Cascade (BRC) that was first published in 1990, it is noteworthy to add GLP-1 receptors to the model (Figure 6). One advantage of the GLP-1 receptor agonists in relation to obesity is that it plays a significant role in inducing insulin secretion after meals and aids in weight loss by encouraging satiety and delaying stomach emptying [36,37]. In addition, GLP-1 receptor agonists have been shown to be very effective at reducing A1c and effective in reducing cardiovascular disease (CVD) in patients with existing ASCVD [38-43]. Research has also shown that GLP-1 receptor agonists have an overall decrease in mortality in people with type 2 diabetes and established CVD [44]. Furthermore, many have begun to take a keen interest in the role of GLP-1 receptors and dopaminergic regulation in the meso-limbic system of the human brain [45] and the potential role of GLP-1 in the attenuation of, for example, alcohol intake from both human genetic association studies and mouse models of alcohol dependence. However, while the agonists to GLP-1 show some positive effects in curtailing food intake [37] and even AUD [45] agonistic effects are very complex. There is also evidence of metabolic adaptation [46].

The patient discovered that the use of a GLP-1 agonist was associated with nearly daily hemiplegic migraines over 60 days, significantly greater than the previous decade where he experienced a hemiplegic migraine maybe once a year. The patient discovered that calcitonin gene-related peptide (CGRP) antagonists worked in opposition to GLP-1 agonists: as GLP-1 agonists stimulate calcitonin release. Furthermore, in a phase IV clinical study of FDA data on the drug Saxenda, migraines were a side effect [47].



Conclusion

This case study serves as a reminder to physicians in practice that it is vital to capture adverse effects early on in the treatment plan. GLP-1 agonists hold promise in obesity and diabetes management but carry risks, especially in patients with neurologic vulnerabilities. If CGRP Antagonists have a counter effect to GLP-1 agonists this should be carefully monitored, and patients should be fully informed of any potential adverse side effects.

Acknowledgements

The authors appreciate the assistance of Danielle Jean Kradin and Margaret A Madigan for their contributions in formatting the paper.

Author contribution

EJM and KB developed the first draft of the article. KUL and AS provided the writing of the abstract and edited the discussion and conclusion. AB developed the schematic. CD developed the references and pkt and RDB added edits and important comments.

Funding

There was no outside funding.

Conflict of Interest

KB is the inventor and through his company synaptamine and Transplicegen Holdings Inc owns USA and foreign patents related KB220 a pro dopamine regulator.

Bibliography

1. Li JR., *et al*. "Case Report: Semaglutide-associated depression: a report of two cases". *Frontiers in Psychiatry* 14 (2023): 1238353.

2. Blum K., *et al*. "Dopamine Lifespan Neuromodulation Wanted Across Brain Reward Circuitry: GWAS Meta And Pharmacogenomic Analyses; 21ST Annual World Congress SMBT, March 15th, (2024).

3. Trujillo J. "Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes". *Journal of Clinical Pharmacy and Therapeutics* 1.1 (2020): 43-60.

4. Ard J., *et al*. "Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists". *Advances in Therapy* 38.6 (2021): 2821-2839.

5. Shyangdan DS., *et al*. "Glucagon-like peptide analogues for type 2 diabetes mellitus". *Cochrane Database of Systematic Reviews* 2011.10 (2011): CD006423.

6. Zheng SL., *et al*. "Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors with All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis". *JAMA* 319.15 (2018): 1580-1591.

7. Elashoff M., *et al*. "Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies". *Gastroenterology* 141.1 (2011): 150-156.

8. Questions and Answers-Safety Requirements for Victoza (liraglutide) [Internet]. U.S. Food and Drug Administration. FDA (2018).

9. Sodhi M., *et al*. "Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss". *JAMA* 330.18 (2023): 1795-1797.

10. He L., *et al*. "Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials". *JAMA Internal Medicine* 182.5 (2022): 513-519.

11. Woronow D., *et al*. "Acute Cholecystitis Associated With the Use of Glucagon-Like Peptide-1 Receptor Agonists Reported to the US Food and Drug Administration". *JAMA Internal Medicine* 182.10 (2022): 1104-1106.

12. Singh S., *et al*. "Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study". *JAMA Internal Medicine* 173.7 (2013): 534-539.

13. Sodhi M., *et al*. "Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss". *JAMA* (2023).

14. Halfdanarson TR and Pannala R. "Incretins and risk of neoplasia". *BMJ* 346 (2013): f3750.

15. Cohen D. "Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed?" *BMJ* 346 (2013): f3680.

16. Butler AE., *et al*. "Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors". *Diabetes* 62.7 (2013): 2595-2604.

17. Egan AG., *et al*. "Pancreatic safety of incretin-based drugs--FDA and EMA assessment". *The New England Journal of Medicine* 370.9 (2014): 794-797.

18. Brooks M. "FDA Sides with EMA on Incretin Diabetes Drugs" (2013).

19. Boess F., *et al*. "Effect of GLP1R agonists taspoglutide and liraglutide on primary thyroid C-cells from rodent and man". *Journal of Molecular Endocrinology* 50.3 (2013): 325-336.

20. Bjerre Knudsen L., *et al*. "Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation". *Endocrinology* 151.4 (2010): 1473-1486.

21. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use OZEMPIC® safely and effectively. See full prescribing information for OZEMPIC. OZEMPIC (semaglutide) injection, for subcutaneous use Initial U.S. Approval: 2017 WARNING: RISK OF THYROID C-CELL TUMORS See full prescribing information for complete boxed warning (2023).

22. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use TRULICITY safely and effectively. See full prescribing information for TRULICITY. TRULICITY (dulaglutide) injection, for subcutaneous use (2023).

23. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use VICTOZA safely and effectively. See full prescribing information for VICTOZA. VICTOZA® (liraglutide) injection, for subcutaneous use Initial U.S. Approval: 2010 WARNING: RISK OF THYROID C-CELL TUMORS See full prescribing information for complete boxed warning (2023).

24. Pradhan R., *et al*. "Exendin-based glucagon-like peptide-1 receptor agonists and anaphylactic reactions: a pharmacovigilance analysis". *The Lancet Diabetes and Endocrinology* 8.1 (2020): 13-14.

25. Bjerre Knudsen L., *et al*. "Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation". *Endocrinology* 151.4 (2010): 1473-1486.

26. Filippatos TD and Elisaf MS. "Effects of glucagon-like peptide-1 receptor agonists on renal function". *World Journal of Diabetes* 4.5 (2013): 190-201.

27. Johansen OE and Whitfield R. "Exenatide may aggravate moderate diabetic renal impairment: a case report". *British Journal of Clinical Pharmacology* 66.4 (2008): 568-569.

28. López-Ruiz A., *et al*. "Acute renal failure when exenatide is co-administered with diuretics and angiotensin II blockers". *Pharmacy World and Science* 32.5 (2010): 559-561.

29. Leehey DJ., *et al*. "Acute Kidney Injury Associated With Semaglutide". *Kidney Medicine* 3.2 (2021): 282-285.

30. Kaakeh Y., *et al*. "Liraglutide-induced acute kidney injury". *Pharmacotherapy* 32.1 (2012): e7-11.

31. Vallatharasu Y., *et al*. "Severe, prolonged thrombocytopenia in a patient sensitive to exenatide". *American Journal of Hematology* 94.3 (2019): E78-E80.

32. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use BYETTA safely and effectively. See full prescribing information for BYETTA. BYETTA ® (exenatide) injection, for subcutaneous use Initial U.S. (2005).

33. EMA statement on ongoing review of GLP-1 receptor agonists (2023).

34. Robin Respaut CT. "Wegovy. Other weight-loss drugs scrutinized over reports of suicidal thoughts" (2023).

35. Tobaiqy M and Elkout H. "Psychiatric adverse events associated with semaglutide, liraglutide and tirzepatide: a pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database". *International Journal of Clinical Pharmacy* (2024).

36. Blum KE and Kozlowski GP. "Ethanol and neuromodulator interactions: a cascade model of reward". *Alcohol and Social Behavior* (1990): 131-149.

37. Perez-Montes DE Oca A., *et al*. "Obesity and GLP-1". *Minerva Endocrinology (Torino)* 46.2 (2021): 168-176.

38. Andreadis P., *et al*. "Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis". *Diabetes, Obesity and Metabolism* 20.9 (2018): 2255-2263.

39. Htike ZZ., *et al*. "Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis". *Diabetes, Obesity and Metabolism* 19.4 (2021): 524-536.

40. Gerstein HC., *et al*. "REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial". *Lancet* 394.10193 (2019): 121-130.

41. Marso SP., *et al*. "SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes". *The New England Journal of Medicine* 375.19 (2016): 1834-1844.

42. Marso SP., *et al*. "LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes". *The New England Journal of Medicine* 375.4 (2016): 311-322.

43. Kanie T., *et al*. "Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis". *Cochrane Database of Systematic Reviews* 10.10 (2021): CD013650.

44. Suchankova P., *et al*. "The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence". *Translational Psychiatry* 5.6 (2015): e583.

45. Hernandez NS., *et al*. "GLP-1 receptor signaling in the laterodorsal tegmental nucleus attenuates cocaine seeking by activating GABAergic circuits that project to the VTA". *Molecular Psychiatry* 26.8 (2021): 4394-4408.

46. Fothergill E., *et al*. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring). 2016 Aug;24(8):1612-9. doi: 10.1002/oby.21538. Epub 2016 May 2. PMID: 27136388; PMCID: PMC4989512.

47. Saxenda and Migraine - A phase IV clinical study of FDA Data. eHealthMe. (n.d.-b). https://www.ehealthme.com/ds/saxenda/migraine/.