

The Ozempic Epidemic: Analyzing Guidelines for Preventing Dependence and β -cell Destabilization in the Treatment of Obesity

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Received September 11, 2024; Revised May 28, 2025; Accepted June 28, 2025

Abstract

Over the past two and a half decades, glucagon-like peptide-1 receptor (GLP-1) agonists, specifically liraglutide and semaglutide, have evolved from an experimental and temporary treatment for type 2 diabetes to a ubiquitous modality for the treatment of obesity and chronic weight gain in all demographics within the United States. The concern in use arises when it is considered that like many other substances that have an effect on the receptors of the human body, semaglutide has not yet been largely analyzed for the possibilities of dependence or withdrawal symptoms that could emerge from the constant use or sudden withdrawal during a cycle of treatment. One of the possible sources from which these dependence or withdrawal symptoms can arise is the uncontrolled β -cell proliferation that surfaces from the decrease in the apoptosis of β -cells. This paper advocated for more in-depth and critical examination of literature on the possible addictive properties that can arise from the proliferation of β -cells whilst using GLP-1 agonists such as semaglutide and the debilitating effects that can ensue, in order to prevent the possibility of a large-scale “epidemic”. This paper investigated the process of β -cell apoptosis under the influence of GLP-1 receptor agonists by organizing a systematic review of previously published literature in order to analyze missing perspectives and research gaps on GLP-1 receptor agonist dependence in humans. The methodology of this paper involved the careful selection of previously published studies which were accessed through Google Scholar in a broad search and subsequently narrowed down using keywords pertinent to the review. Throughout this selection process, a PRISMA Flow Diagram was utilized to identify, screen, and ultimately include the resulting studies which were reviewed. Through the synthesis of existing studies with novel perspectives, this paper aimed to seal the gap for dependence in the use of GLP-1 receptor agonists by proposing new guidelines and examining overlooked aspects in the prescription and use of GLP-1 receptor agonists. The results of this paper featured a set of three distinct guidelines on the prescription and administration of GLP-1 receptor agonists that provide potential conduct for future studies and advancements in the field of medicine.

Keywords: Semaglutide, Medicine, Healthcare, GLP-1 Agonist, β -cells, Dependence, Obesity

1. Introduction

According to the National Institute of Health (NIH) an obese person can be defined as a person whose weight is higher than what one could consider a “normal” weight for a given height measurement (NIDDK, 2021). Statistics released from the TFAH State of Obesity 2023 Report showed that approximately 41.9% of adults in the United States are obese (Farberman, 2023). When considering a weight that is higher than a perceived “normal” weight for a given height, there is a scale that is used to make sure that trends stay consistent and do not vary depending on different demographics or social situations. The Body Mass Index (BMI) scale is a number scale that is used to estimate and record obesity in adults (NIDDK, 2021). A specific BMI is calculated by the weight of a person in kilograms divided by their approximate height in meters squared (NIDDK, 2021). By using the generalized formula for BMI, standards for healthy weight-to-height ratios are able to be set. The current standards that are present on the BMI scale define a

person that is healthy weight as being within the BMI range of 18.5-24.9, an underweight person as having any BMI less than 18.5, an overweight person as being within the BMI range of 25-29.9, and an obese person as being any BMI more than 30.

As obesity rates in the United States climb, people have been desperately searching for ways to reduce weight gain. The problem arises when it is taken into consideration that the majority of people want to lose weight without putting in any effort to better their lifestyle. This leads to a progression of weight gain that can eventually unravel a plethora of health problems in one's future. Being obese slowly deteriorates the functioning and well-being of one's body. The reason for this is consistent with the fact that carrying extra fat in the body could potentially lead to adverse effects such as cardiovascular disease, type 2 diabetes (T2D), potential cancers, and musculoskeletal disorders (WHO, 2024).

When the FDA granted approval to Novo Nordisk in 2017 to produce a semaglutide 1 mg injection (Ozempic) for the treatment of T2D, many realized the adverse effect of weight loss that presented with consistent use of the injection (FDA, 2021). Semaglutide is a GLP-1 agonist that activates adenylyl cyclase in the β -cells of the pancreas, thus increasing insulin production (WVU, 2017). Consistent with the tendencies of other GLP-1 agonists, the use of semaglutide results in reduced appetite (WVU, 2017). Other GLP-1 agonists were experimented with and used as their effectiveness became more prevalent, but the stronger and more efficacious albumin binding allowed semaglutide to maintain a much longer half-life than earlier GLP-1 agonists such as liraglutide (Lau et al., 2015). It was observed that through a non-covalent bond to albumin, semaglutide maintained a half-life of 165-184 hours (WVU, 2017).

The backbone for the mechanism of action of semaglutide is β -cells. According to Tamayo-Trujillo et al., "GLP-1 activation increases neogenesis and proliferation while decreasing apoptosis of pancreatic β -cells" (p. #2). Due to the fact that GLP-1 agonists mimic the activation of GLP-1 receptors, it can be inferred that the use of semaglutide increases neurogenesis and proliferation while at the same time decreasing the series of death of the β -cells. The concern is present in the fact that this could subsequently lead to hypoglycemia and disruption of the glucose homeostasis process due to shifts in the islet cell population. (Cerf, 2013). With this process, it can be hypothesized that the human body and its natural functions could become dependent on the drug in order to work towards maintaining glucose homeostasis and stable insulin levels.

While there are previous studies which have examined the adverse effects of the use of GLP-1 receptor agonists, the majority of the studies lack insight on the qualities of dependence that can be derived from GLP-1 receptor agonists. For example, the study conducted by Gaur in 2023 resulted in extraordinarily useful data on the qualities of dependence that could be present in mice who had been administered drugs similar to semaglutide, but the study left the findings open-ended and lacked further analysis on how this could transmit to qualities of dependence in humans as well. This analytical gap limits the ability for data derived from the study to be further utilized in future studies and experiments on GLP-1 receptor agonist dependence in humans. Addressing this gap is vital because the data found in previous studies could be utilized to begin additional detailed studies on how alterations in use on mice could be transmitted in alterations to use in humans. This could allow for potential decreases in the risk of dependence that humans experience with use of GLP-1 receptor agonists. This paper contributed to this research gap by bridging the open ends of the previous literature with a systematic review and guidelines that could change the path of GLP-1 receptor agonists prescription and administration in future cases.

The objective of this paper was to set out that specialists, researchers, and scientists who are involved in the production and distribution of GLP-1 agonists like semaglutide acknowledge the adverse effects from semaglutide on β -cells in order to set forth a series of guidelines that can be implemented to reduce the risk of unnecessary exposure and damage that could come with the misuse and overprescription of said drug. By limiting the use of semaglutide to a certain population that relies on the drug for the treatment of T2D rather than for the population that "recreationally" uses the drug to manage obesity, the medical community could get ahead in preventing a potential "epidemic" that could arise from the damage and destabilization of the β -cell process that the body relies on to properly function.

2. Materials and Methods

A systematic review conducted using Google Scholar identified papers that had relevance to the topics of

medicine, healthcare, patient care, semaglutide, β -cells, and insulin production. PRISMA guidelines were referred to. The keywords and phrases searched for included “semaglutide”, “GLP-1 Agonist”, “ β -cells”, “ β -cell apoptosis”, “insulin”, and “insulin production”.

The 3 stages of identification, screening, and inclusion from the PRISMA guidelines were utilized as the basis of decision throughout the selection process. The selection process began with the identification stage where a search was conducted using the Google Scholar database and the keywords listed previously. A total of over one thousand records were identified. Following the initial search, any duplicate records were removed and any records marked as ineligible by the database automation service were removed. The results were condensed to papers published from the last 12 years and approximately one thousand records remained. After the identification stage had been completed, the screening stage began. Each page of records was scanned and any documents that were published in a foreign language or only briefly referenced the selected keywords as support for an irrelevant topic were discarded. Following the first stage of the screening process, 13 papers were deemed as fitting for the incorporation criteria. The second stage of the screening process involved searching for any previously discarded documents during the first screening stage that could be retrieved and deemed useful. In addition, any records that provided conflicting results which could be used in data comparisons were reviewed, but it was deemed that no previously removed records contained any applicable conflicting results. No previously discarded papers were retrieved for supporting arguments or conflicting arguments. Once the second stage of screening had been complete, the third stage of screening began where each of the 13 records was assessed for eligibility in the systematic review. Each record was read multiple times and considered equally among the other articles. It was decided that only the records whose thesis and supporting evidence directly involved the correlation between GLP-1 receptor agonists, β -cells, and insulin production should be included. The final stage of the screening process had been completed, and the remaining records were compiled for the inclusion stage. Conclusively, three high-caliber papers were assimilated in order to properly address concerns on β -cell process destabilization and development of dependence, as well as derive a series of guidelines that could be implemented.

3. Representative Case Studies

The adverse effects of GLP-1 agonists like semaglutide have been documented in few case publications to this date. Said few publications, however, contain extremely valuable discussions on the topic and reinforce the need for safety guidelines. One illustration of this was shown through *ex vivo* and *in vitro* investigations on mice involving the effect of GLP-1 receptor agonists on the sorting of the receptor, which controls the effectiveness of the GLP-1 receptor agonist (Gaur, 2023). By doing so, researchers were able to reveal valuable findings on the understanding of the development of dependence for investigated drugs such as semaglutide, and specific biases that could be used to prevent the development of dependence (Gaur, 2023). It was found that by biasing incretin drugs such as semaglutide for G protein (a messenger protein used to elevate cAMP levels and increase insulin secretion) and away from arrestin (adaptor proteins that regulate receptor sorting and increase insulin secretion) engagement, it is possible to prevent dependence (Gaur, 2023).

4. Results

As the medical and healthcare fields progress and semaglutide continues to prevail and become a popular “shortcut” to rapid weight loss, it is important all the more to set forth a series of guidelines that can be implemented to reduce the risk of damage that can be derived from unregulated use. With this drug in particular presenting weight loss and improved glucose control, it is also vital to note that such therapeutic benefits require scheduled use and will eventually diminish with time (Gaur, 2023). This “development of dependence” and possible destructive effect on the β -cell process leads to major concerns about what some may call the “recreational” use of the drug.

A controlled *in vivo* study conducted by Gaur in 2023 examined the development of tolerance towards incretin drugs in wild type mice when injected subcutaneously with a low dose of glucose (5.5 mM), a high dose of glucose (11 mM) and a high dose of glucose plus Exenatide (11 mM + Ex-4), a shorter acting GLP-1 receptor agonist compared to semaglutide. In addition, the results of wild type mice with GASP-1 knocked out in β -cells were examined to

observe if GASP-1 interaction had any statistical significance in secretion of insulin over time. The experiment involved an acute period (short-term), a tolerance period (following 3 hours of injecting Exenatide), and a recovery period (following a 24-hour recovery frame). It was observed that a noticeable difference in the amount of insulin secretion during the tolerance periods of the base wild type mice and the wild type mice with GASP-1 knocked out in β -cells. The data recorded shows that for the wild type mice with GASP-1 knocked out in β -cells, the secretion of insulin was approximately 1.5 nM, 3 nM, and 5.8 nM for the low dose, high dose, and high dose + Ex-4 treatment groups respectively. Almost identical results were recorded for the acute period, tolerance period, and recovery period, showing no development of tolerance. In the base wild type mice, the data recorded shows that the secretion of insulin was approximately 1 nM, 3 nM, and 5.5 nM for the low dose, high dose, and high dose + Ex-4 respectively. For the tolerance period, the secretion of insulin was approximately 1.2 nM, 3.2 nM, and 3.1 nM for the low dose, high dose, and high dose + Ex-4 respectively. For the recovery period, the secretion of insulin was approximately 1.1 nM, 2.2 nM, and 4.5 nM for the low dose, high dose, and high dose + Ex-4 respectively. The significant decrease in insulin secretion shown in the tolerance and recovery period suggests a development of desensitization due to either GLP-1R downregulation or altered trafficking in the signaling pathway. The data present above that was recorded in Gaur's *in vitro* experiment on mice support the hypothesis that the administration of a GLP-1 receptor agonist could potentially lead to the development of tolerance and dependence, resulting in decreased levels of insulin secretion.

While the study conducted by Cerf in 2013 does not directly address the development of tolerance to GLP-1 receptor agonists, it highlights the impact of β -cell integrity and the regulation of metabolic processes. The results of the study shows that the presence of high saturated fats in the bloodstream of an individual can signal competition between glucose and saturated fats for uptake and metabolism in tissue cells. This is likely due to the desensitization of glucose recipient organs in the human body as a result of increased GLP-1 receptor use. The results of this study conducted by Cerf parallel the more recent study conducted by Gaur in 2023 where it was concluded that the secretion of insulin in mice can be directly desensitized by the administration of GLP-1 receptor agonists over a distinct period of time. While Gaur's study took an *in vivo* approach and analyzed the results in a quantitative manner, Cerf's study provides qualitative support on the potential for desensitization and disruption of the β -cell and insulin regulation process. Due to the lack of additional studies with quantitative results in a supportive or contradictory approach in relation to Gaur's 2023 study, there are no numerical trends or differences that can be associated between studies.

After the evaluation of several different scholarly articles, 3 clear-cut guidelines for the use of semaglutide have been composed.

4.1 Guideline 1: Ensuring Healthcare Providers Are Aware of Possible Development of Dependence to Semaglutide

It should be well known by all healthcare providers who are in the position of prescribing mechanism-altering drugs that the β -cell regenerative capacity is one that has been shown to appear limited in humans (Saisho, 2015). The mechanism of action of semaglutide has the ability to stimulate epidermal growth factor, therefore triggering phosphatidylinositol-3 kinase, and furthermore initiating transcription factors associated with β -cell growth and hindering transcription factors associated with β -cell apoptosis (Tamayo-Trujillo et al., 2024).

With the proliferation of the β -cells being stimulated from the semaglutide, there is a risk that the levels of insulin that are being secreted could increase to an undesirable level, resulting in hypoglycemia (Cerf, 2013). In addition, other islet cell types that secrete certain hormones that assist in maintaining glucose homeostasis may lose functionality due to the proliferation of β -cells (Cerf, 2013). With this in mind, healthcare providers must be educated in order to ensure that they are aware of the mechanism of action of semaglutide and how it can create dependence, hypoglycemia, and other adverse effects that may not be worth the risk. Instead, healthcare providers can look for alternative tactics and referrals that would benefit the person seeking weight loss, while not risking the damage of their body's β -cell process by prescribing a drug that is targeted for the treatment of patients with T2D.

4.2 Guideline 2: Provide Proper Patient Education Courses on the Mechanism of Action and Potential Risks of Semaglutide

In many fields of healthcare and medicine, it is crucial to brief patients on certain procedures, tests, or simple

situations that they may be going through in the future as part of their treatment and are not well educated on. Healthcare and medicine providers spend years learning the depth of medicinal knowledge so that the patient can be safe and hold trust in their providers. Unfortunately, it cannot be assumed that all providers will take the time to find all possible treatments for the patient and educate them on each and every single one. On the other hand, it is completely plausible for providers to educate patients on the mechanism of action of semaglutide and the possible adverse effects that can come from its use for weight loss.

Once the patient is fully educated on what they will be administering to their own body, they will then be able to weigh out the risks of other possible treatments, such as mild exercise for weight loss. This educated decision-making will not only save the patient the risk of developing dependence on a drug that they may not definitively need, but it will also steer them to make active changes to their lifestyle that they will be able to carry over once the treatment of their medical concern has been treated to the best of one's ability. If the provider feels that the best possible treatment for the patient is semaglutide and the patient makes an educated agreement, then it is certain that both the provider and the patient agree on a single path that will keep the patient safe and bring them progress.

4.3 Guidelines 3: Additional Research on Alternatives Such as GASP-1 Interaction in Order to Reduce the Potential for the Destabilization of the β -cell Balance

The fields of medicine and healthcare advance at such a rapid pace each and every single day that it is almost impossible to slow down the discovery of novel drugs and treatment strategies. In the time that researchers spent investigating liraglutide, they were able to stumble upon semaglutide and its unique structure. These simple novel discoveries are what guide the healthcare and medicine fields and allow them to advance.

Semaglutide's prevalence over other GLP-1 agonists is attributed to its structural development from liraglutide and perceived prolonged effectiveness due to advanced pharmacokinetic analysis. As a GLP-1 agonist, semaglutide increases insulin production by the stimulation of adenylyl cyclase in the beta cells of the pancreas (WVU, 2017). In addition, it also migrates to the brain to suppress appetite and slow the emptying of the stomach (WVU, 2017). These characteristics of semaglutide have not only resulted in an exponential increase in the use and prescription of GLP-1 agonist for the treatment of type 2 diabetes over the past couple of years, but it has only resulted in the deviation in the use of semaglutide, now being used for "lose weight quick" schemes.

Ex vivo and in vitro studies have been conducted on mice in order to test possible alternatives to semaglutide that could eliminate the risk of the development of dependence. One of the most enlightening studies found a crucial property of G-protein coupled receptor-associated sorting protein 1 (GASP-1) that could be further researched to limit the possibilities of dependence development. It was found through the *ex vivo and in vitro* studies that it is potentially possible to target GASP-1 and the interactions that it has with GLP-1 receptors in order to derive a therapeutic mediation with the goal of limiting the development of dependence and increase the overall productivity of the drug (Gaur, 2023).

By thoroughly analyzing research on GASP-1 interaction, professionals in the healthcare and medical fields, the possibility of the discovery of a novel and revolutionary process would increase exponentially.

5. Discussion

Humans are naturally drawn to the quickest and most efficient ways to get tasks completed. This is primarily due to the evolution of human behavior over time for survival and prosperity. In some cases, the desire and instinct for these quick and efficient ways lead to a figurative blindness of external factors. Due to the short time and experience that humans are allowed in their one life, desperation and distress build on this blindness and encourage shortcuts to task completion, even if it results in skipping over important precautions and warnings.

Obesity is an issue that affects more than one billion people worldwide. On a national scale, it is one of the most prevalent and habitually predisposed physical conditions that must be addressed. What sets obesity apart from other physical conditions is that, excluding genetic conditions and illness, it can be treated through not only medications like semaglutide but daily activities such as exercise as well. The early research on medicinal treatment for obesity has led to the "recreational" use of drugs like semaglutide. The use is "recreational" in the context that it is not needed

in many cases. It can be seen as one of those shortcuts that are used to achieve a long-term goal in a short period of time. Obviously, this is not a perfect world, and not everyone is able to exercise every day and spend extra time and money preparing a special diet, hence, the use of medications like semaglutide. The problem arises when it is taken into consideration that the primary target of semaglutide in treatment is for patients that have T2D. There have been few cases of extremely harmful or fatal cases that develop from the “recreational” use of medications like semaglutide, but there are still possible adverse effects such as hypoglycemia, the development of dependence, and the disruption of the β -cell process that can derive from said use. Due to the possible impact of these adverse effects, it is of vital importance that medical professionals follow the proper restrictive guidelines on the prescription and use of semaglutide in order to ensure that conservative treatment is being administered in a decisive and effective manner.

Semaglutide works by increasing insulin production by the stimulation of adenylyl cyclase in the beta cells of the pancreas and migrating to the brain to suppress appetite and slow the emptying of the stomach. This not only makes the drug desirable in the treatment of T2D but also works as an effective treatment for obesity. The problem is that the use of semaglutide can lead to the uncontrolled proliferation of β -cells in the human body. This not only risks the destabilization of glucose homeostasis but can also prioritize the use of β -cells almost entirely over other islet-type cells. In addition, the development of dependence with the use of the drug has been observed and shows a progressive pattern of increase as use is continued. The recommended guidelines were formulated in order to attempt to provide a ubiquitous plan of treatment for obesity that keeps the patient safe while still maximizing the potential of medication use for weight loss.

By ensuring that healthcare providers are aware of the possible development of dependence to semaglutide, they will not only be able to educate the patient on the possible risks of using the drug but will also be able to have the willingness to look for other possible treatments that can be beneficial to the patient without carrying as many risks. If this pattern is followed by the majority of healthcare providers around the nation, it can be inferred that the trend of exponential increase in the use of semaglutide for weight loss could reach a plateau and maybe eventually decrease due to the discovery of a safer alternative. In addition, this adaptation to a mindset of awareness could decrease the number of providers that are prescribing medication simply to provide a simple and easy solution to the patient. The healthcare provider is the gateway between the patient and the drug. Because of that, it is important that they are using their own educated discretion and decision-making with the knowledge that the drug can be addictive.

When it comes to providing proper education for patients who are considering using semaglutide, it is important to note that for many risky procedures and actions in the medical field, the patient is educated on the important aspects so that they are making a fully educated decision on what they are about to undergo. The same should be the case when it comes to taking semaglutide. Semaglutide has the potential to become an addictive drug that can affect the stability of the body and its different processes, so it is important to make sure that the patient is aware of the adverse effects that could occur with the medication. By providing a specific generalized education course on semaglutide, the patient will be able to consider alternatives for their treatment that may be better for them in the long term.

Finally, by encouraging providers to promote research on GASP-1 interaction, the possibility of a potential novel drug discovery would increase noticeably. The healthcare and medical fields are known to advance through the production and analysis of research. The majority of the providers who are professionals in the healthcare and medical fields have spent multiple years of their lives studying and preparing to obtain the best base of knowledge for the treatment of humans that they possibly could. When you take many of these brilliant minds and have them work towards a single goal, progress is able to take place at an exponentially faster rate. The studies on alternatives to semaglutide, like GASP-1, are limited due to how popular the drug has been recently. If progress towards low dependence and more stability were able to be seen through *ex vivo* and *in vitro* studies on mice, it is only time before something is discovered for humans. All that is needed is for the healthcare and medical fields to assemble as a whole in order to make these advances as quickly as possible. Each second that is spent progressing towards the safety of a patient is a second well spent, even if many people see the current treatment to be working well.

As these recommendations are put forth, it is vital to be aware that the production and distribution of medication relies not only on the healthcare and medical providers, but on the complex industry of pharmaceuticals as well. We understand that there is also business and livelihood to be made from the production and distribution of medication in the healthcare, medical, and pharmaceutical industries. What we need to stress is that what brings all of these fields

together is the well-being of not only individual humans but society as a whole. Humans should not be concerned that their treatment is based on the patterns of how successful a drug is on the business side of these fields, but rather they should be held assured that all providers in each and every single one of these industries will always prioritize the patient and find them the safest and most effective solution. This needs to be taken into consideration on the topic of semaglutide so that the use of medication to treat obesity in the United States does not evolve into a dependence-driven “epidemic”.

6. Conclusion

Simply disregarding the potential risk that comes with the increasing trends of semaglutide will not assist the future of healthcare and medicine. Instead, it will generate chronic symptoms that force patients to be reliant on their medication in order to maintain proper health. This paper examined the quantitative and qualitative results of various studies in order to derive a total of three guidelines which can be implemented in order to regulate the use of GLP-1 receptor agonists. With limited studies previously conducted on GLP-1 receptor agonists and their adverse effects on the β -cell process and insulin regulation cycle, this paper compiled results from each quantitative and qualitative study in order to ensure a complete systematic review and analysis. The results of the complex analysis show that there is a significant increase observed in previous *in vivo* experiments that can be attributed to the disruption of regulation cycles in insulin secreting cells. These data points were analytically compared to qualitative data on potential β -cell cycle disruption in human tissue cells from GLP-1 receptor agonist and it was confidently deduced that the impact on insulin secretion mice cells from the *in vivo* study could occur in human tissue cells as well, resulting in the development of tolerance and dependence. The guidelines suggested in this paper sought to ensure that healthcare providers become aware of the adverse effects that can be derived from GLP-1 receptor agonists, confirm that patients are properly informed by their care providers of the potential to develop dependence on GLP-1 receptor agonists, and promote additional research on how GLP-1 receptor agonist alternatives such as GASP-1 could provide more security in the stabilization of β -cell processes. By implementing guidelines, a basis will be set for all providers around the nation so that they can branch off using the skills and tools that they have to create a more secure and efficient form of treatment. As society moves into the future, it is imperative that the healthcare system stays one step ahead in order to prevent the cataclysmic medicinal “epidemics” that society has not only witnessed in the past but also experienced. This collaborative effort will not only instill a deeper trust in the healthcare system and its professionals but also provide a further example of the progressive changes that can be made when the healthcare unites to amplify ideas into reality.

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