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GLP-1 agonists: A review for emergency clinicians

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Abstract

Introduction

Glucagon-like peptide 1 (GLP-1) based therapies, including GLP-1 agonists, are currently in use for treatment of diabetes and obesity. However, several complications may occur with their use.

Objective

This narrative review provides a focused evaluation of GLP-1 agonist therapy and associated complications for emergency clinicians.

Discussion

GLP-1 agonists potentiate insulin release and reduce gastric emptying and food intake. These agents have demonstrated significant improvements in glucose control in diabetics and weight loss in obese patients. The two most common agents include subcutaneous semaglutide (Ozempic, approved for type 2 diabetes, and Wegovy, approved for weight loss) and liraglutide (Saxenda, approved for weight loss, and Victoza, approved for type 2 diabetes), though an oral formulation of semaglutide is available (Rybelsus). While these drugs are associated with improved long-term outcomes, there are a variety of associated adverse events. The most common include gastrointestinal (GI) adverse events such as nausea, vomiting, diarrhea, and abdominal pain. Pancreatitis and biliary disease may also occur. Hypersensitivity including injection site reactions have been associated with use, with reports of anaphylaxis and other rashes. Renal adverse events are most commonly associated with severe GI losses. Hypoglycemia may occur when these agents are used with sulfonylureas or insulin. There is also an increased risk of diabetic retinopathy. Due to the current shortage and expense of these medications, many patients have attempted to obtain these medications from non-licensed and unregulated agents, which may be associated with increased risk of serious complications.

Conclusions

An understanding of the indications for GLP-1 agonist use and associated adverse events can assist emergency clinicians.

Introduction

Obesity affects over 40% of United States (U.S.) adults, with over 11% of the American population suffering from diabetes [1]. Both conditions are associated with complications and decrease in life expectancy [1,2]. Glucagon-like peptide 1 (GLP-1) based therapies including GLP-1 receptor agonists, dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors have been in use for years for treatment of type 2 diabetes mellitus (DM2) due to their impact on glucose control [[3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29]]. GLP-1 agonists are increasingly used for diabetes and weight loss, with several recognized complications, and emergency clinicians must be able to recognize and manage these complications [[26], [27], [28], [29], [30]].

GLP-1 is an incretin hormone produced from the L cells of the small intestine that binds to the GLP-1 receptor (GLP-1R). This receptor is expressed by the pancreatic beta cells and ducts, gastric mucosa, lungs, heart, kidneys, immune cells, and hypothalamus [[3], [4], [5], [6],[12],[19],29,30]. GLP-1 primarily stimulates glucose-dependent release of insulin from the pancreatic islets. GLP-1 agonists reproduce and enhance the effects of natural GLP-1 [[3], [4], [5], [6],[12],[19]. Subsequently, GLP-1 potentiates insulin release when glucose levels are elevated after meals, reduces gastric emptying and food intake due to increased feelings of satiety, inhibits release of inappropriate post-meal glucagon, and has direct effects on the central nervous system (i.e., hypothalamus, nucleus accumbens, ventral tegmental regions, and vagus nerve) including hunger control and reducing inflammation. In doing so, GLP-1 can assist in glucose control in diabetes and lead to weight loss. Importantly, GLP-1 agonists are also associated with improved ejection fraction, coronary blood flow, and cardiac output while reducing the risk of cardiovascular events, infarction size, and all-cause mortality [3,22], [23], [24], [25]. The half-life of GLP-1 is 1–2 min due to metabolism by dipeptidyl peptidase 4 (DPP-4), though synthetic GLP-1 agonists have longer half-lives due to variable metabolism by DPP-4 [[30], [31], [32], [33], [34], [35], [36], [37]].

The most common GLP-1 agonists used in the U.S. include semaglutide (Ozempic, U.S. Food and Drug Administration [FDA] approved for DM2 by subcutaneous [SQ] injection; Wegovy, FDA-approved for weight loss by SQ injection; and Rybelsus, FDA approved for DM2 by oral route), liraglutide (Saxenda, FDA-approved for weight loss by SQ injection, and Victoza, FDA-approved for DM2 by SQ injection), and tirzepatide (Mounjaro, FDA-approved glucose-dependent insulinotropic polypeptide [GIP] receptor and GLP-1 agonist for DM2 by SQ injection) (Table 1) [[30], [31], [32], [33], [34], [35], [36], [37]]. Tirzepatide is currently under review by the FDA for weight loss. Dulaglutide (Trulicity, FDA-approved for diabetes) and albiglutide (Tanzeum, FDA-approved for diabetes) are older GLP-1 agonists, though Tanzeum has been discontinued [38].

GLP-1 agonists are approved for patients with a body mass index (BMI) ≥ 30 and those with BMI ≥ 27 and a weight-related condition (e.g., diabetes, hypertension, etc.). Multiple studies suggest these medications are associated with approximately a 15% reduction in weight over 1–2 years [[3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25]]. Based on these results, the American Gastroenterological Association issued a practice guideline in November 2022 recommending that semaglutide 2.4 mg be utilized for treatment of obesity over other pharmacologic treatments [25]. There are several contraindications to the use of GLP-1 agonists, including serious hypersensitivity reaction to a GLP-1 agonist and pregnancy. GLP-1 agonists are not recommended in those with personal or family history of multiple endocrine neoplasia 2A; multiple endocrine neoplasia 2B, or medullary thyroid cancer due to concern for long-term thyroid effects, though data in human studies are lacking [[31], [32], [33], [34], [35], [39], [40], [41], [42], [43]]. Patients with significant GI conditions including gastroparesis and inflammatory bowel disease should also avoid these agents, as should those with prior pancreatitis.

Section snippets

Methods

To construct this narrative review, the authors searched PubMed and Google Scholar for articles using a combination of the keywords "GLP-1 agonist" OR "semaglutide" OR "liraglutide" AND "adverse event" OR "side effect". The search was conducted from the databases' inception to October 20, 2023. PubMed yielded over 2,800 articles. Authors evaluated case reports and series, retrospective and prospective studies, randomized controlled trials (RCTs), systematic reviews and meta-analyses, other ....

Gastrointestinal complications

Adverse events are common in those using GLP-1 agonists [[26], [27], [28], [29]]. These most commonly include GI side effects, which occur in up to 70% of patients and appear to increase with higher doses [6,[26], [27], [28], [29],44,45]. Typical GI adverse events include nausea (most common), vomiting, and diarrhea [[26], [27], [28], [29],44,45]. Other GI side effects include decreased appetite, abdominal pain, dyspepsia, and constipation. Literature suggests semaglutide has the greatest ....

Conclusions

GLP-1 agonists are an increasingly common treatment for DM2 and for weight loss in those with obesity. Their use is associated with improved glucose control and weight loss, but there are several associated adverse events. GI effects are most common, including nausea, vomiting, diarrhea, and abdominal pain. Other adverse events include hypersensitivity reactions, rash, renal adverse events such as AKI, and diabetic retinopathy. Patients should only obtain medications from a licensed care ....

CRediT authorship contribution statement

Brit Long: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Data curation, Conceptualization. **Jessica Pelletier:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources. **Alex Koyfman:** Writing – review & editing, Validation, Supervision, Resources, Data curation, Conceptualization. **Rachel E. Bridwell:** Writing – review & editing, Visualization, Validation, Resources, Formal analysis, Conceptualization. ...

Declaration of competing interest

None.

None of the authors have submitted a review on this topic or published previously on this topic.

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