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Evaluating the Efficacy of GLP-1 Receptor Agonists in Prader-Willi Syndrome: A Review of Case Series

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ABSTRACT: Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by hyperphagia, obesity, and metabolic complications including diabetes mellitus. Managing these symptoms is challenging because of the syndrome's multifaceted nature. Glucagon-like peptide-1 (GLP-1) receptor agonists, known for their efficacy in diabetes and weight management, have emerged as potential therapeutic agents for PWS. **Methods:** This review synthesizes findings from PubMed-indexed case reports on GLP-1 receptor agonists in patients with PWS. Articles were selected based on specific criteria that focused on changes in weight, glycemic control, and hyperphagia. The effects of these agents, both as monotherapy and in combination with other drugs, were analyzed. **Results:** Four case reports met the inclusion criteria and highlighted significant clinical outcomes. Treatments with GLP-1 receptor agonists were associated with notable weight loss, reductions in HbA1c, and improved control of hyperphagia. Cases varied in treatment duration and combinations but consistently showed positive effects on PWS's primary symptoms. **Conclusion:** GLP-1 receptor agonists represent a promising therapeutic option for managing core symptoms of Prader-Willi syndrome, particularly when traditional treatments have failed. Further research is essential to establish long-term safety and efficacy and guide optimal therapeutic strategies for this challenging syndrome.

1. INTRODUCTION

Prader-Willi syndrome (PWS) is a complex genetic disorder caused by the absence of paternal gene expression in the chromosomal region 15q11-q13 [1]. PWS is characterized by a spectrum of physiological and behavioral anomalies, including hyperphagia, obesity, hypogonadism, growth hormone deficiency, cognitive impairment, and challenging behaviors [2]. The syndrome was first described by Prader, Labhart, and Willi in 1956 and remains a significant challenge in medical management due to its complicated nature and the severe morbidity associated with its symptoms, particularly obesity and its metabolic consequences [3]. One of the most distressing and life-threatening symptoms of PWS is hyperphagia, a relentless, insatiable appetite that leads to chronic overeating and life-threatening obesity [4]. This uncontrolled eating behavior is caused by a dysfunction in the hypothalamic region that typically regulates hunger and overfilling [5]. Consequently, individuals with PWS experience an almost continual urge to eat, coupled with a decreased caloric expenditure, which further complicates obesity management and leads to early-onset morbid obesity [6]. This phenotype is particularly challenging to manage because standard weight-loss strategies, such as dietary restrictions, lifestyle modifications, and pharmacotherapy, often prove insufficient.

Alongside the complications arising from obesity, individuals with PWS frequently develop type 2 diabetes mellitus (T2DM), which further complicates the clinical management of these patients [7]. The risk of developing diabetes in the PWS population is exacerbated not only by severe obesity but also by intrinsic insensitivity and an impaired pancreatic beta-cell function, aspects that require innovative therapeutic approaches beyond conventional diabetes management strategies [8]. Recent advances in pharmacotherapy have introduced glucagon-like peptide-1 (GLP-1) receptor agonists as a potential treatment modality for managing both hyperphagia and metabolic dysfunctions in PWS [9, 10]. GLP-1 is a hormone involved in glucose homeostasis, which enhances insulin secretion, inhibits glucagon release, and delays gastric emptying [11]. Therefore, beyond glycemic

control, GLP-1 receptor agonists have shown promise in weight management by reducing appetite and food intake, addressing the core phenotypical challenges of PWS.

The rationale for using GLP-1 receptor agonists in PWS is underpinned by their dual action on the pathways implicated in the syndrome's pathophysiology [12]. The weight-loss effect of GLP-1 receptor agonists can be particularly beneficial in controlling the obesity prevalent in PWS patients [13]. The mechanism involves delayed gastric emptying and enhanced satiety through central pathways, which helps mitigate the uncontrolled eating behaviors characteristic of PWS [14]. Improved insulin sensitivity and enhanced beta-cell function contribute to better glycemic control, which is crucial for managing diabetes in these patients [15]. Moreover, accumulating evidence from case reports supports the use of GLP-1 receptor agonists in PWS, offering a new therapeutic option where traditional treatments have failed [9, 16, 17]. These case studies provide essential understanding of the practical applications and outcomes of GLP-1 receptor agonists, highlighting significant improvements in hyperphagia control, weight reduction, and metabolic stability.

This paper reviews the emerging role of GLP-1 receptor agonists in managing Prader-Willi syndrome, focusing on their impact on glycemic control and weight management. Through a detailed examination of recent case reports and series, this review aims to elucidate the effectiveness of these agents in real-world clinical settings, their therapeutic potential, and the implications for future treatment strategies for individuals afflicted with PWS.

2. MATERIALS AND METHODS

2.1 Study Design

To assess the efficacy and safety of glucagon-like peptide-1 (GLP-1) receptor agonists in managing Prader-Willi syndrome (PWS), we conducted a detailed literature search in PubMed. This systematic review aimed to collate and analyze relevant literature on the clinical use of GLP-1 receptor agonists in patients with PWS, particularly their effects on glycemic control and obesity management.

2.2 Literature Search Strategy

The search used a specific keyword strategy to capture all case reports. The keywords used were "Prader-Willi syndrome" and "Glucagon-Like Peptide-1 Receptor Agonists." These terms were combined in the search query as "(Prader-Willi syndrome) AND (Glucagon-Like Peptide-1 Receptor Agonists)" to filter articles that discuss the application of GLP-1 receptor agonists specifically in the context of PWS.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria were as follows: articles had to be written in English, involve patients diagnosed with Prader-Willi syndrome, discuss the use of GLP-1 receptor agonists, and include clinical outcomes such as changes in weight, appetite, glycemic control, or other metabolic parameters. Both full articles and abstracts were considered, provided they offered sufficient data on these outcomes. Exclusion criteria included articles not in English, studies not involving human subjects, publications not focused on Prader-Willi syndrome, and non-empirical articles such as narrative reviews, commentaries, and editorials. Data from each relevant article were extracted, focusing on study author(s), year of publication, study design (whether case report or case series), the number of participants with PWS, their age and gender, the specific type of GLP-1 receptor agonist used, dosage, duration of treatment, and noted clinical outcomes. This process also involved noting any side effects reported in the studies. One reviewer initially extracted data from each article, and another cross-verified it to ensure accuracy and reliability.

The synthesis of the extracted data was qualitative, summarizing the therapeutic outcomes from the use of GLP-1 receptor agonists in PWS. This approach facilitated a comprehensive understanding of the efficacy of these treatments in real-world settings and helped identify any gaps in the current research. The review adhered to ethical guidelines for secondary data analysis, focusing on ensuring the accuracy and integrity of information extracted from primary sources. However, no ethical approval was required because the review did not involve new studies of human or animal subjects. Ethical approval was not required because this review analyzed publicly available, de-identified data from existing case series on Prader-Willi Syndrome.

2.4 Consent statement

This case series is based on previously published case studies. As per the CARE guidelines, patient consent for publication was obtained in the original studies. No new patient data were collected or reported in this case series.

3. RESULTS AND DISCUSSION

3.1 Study Selection

The systematic search of the PubMed database revealed four case reports that met the inclusion criteria for the review. These cases provided substantive insights into the efficacy of glucagon-like peptide-1 (GLP-1) receptor agonists in managing Prader-Willi syndrome (PWS), particularly their effects on weight management, glycemic control, and hyperphagia. The collected data, including patient demographics, treatment regimens, duration, and clinical outcomes, were summarized in a comprehensive table to support detailed analysis and comparison across case scenarios.

The cases varied in patient age, gender, treatment specifics, and duration, providing a diverse overview of the clinical applications of GLP-1 receptor agonists. A summary of these details, along with the observed clinical outcomes, is provided in [18]. This case involved an adult male treated with a combination of exenatide and liraglutide over a duration of 10 years. The treatment resulted in a significant weight loss of 125 lbs and a decrease in HbA1c from 7.4% to 5.7%. This case demonstrates the potential for long-term GLP-1 receptor agonists to sustain improvements in obesity-related complications associated with PWS. Sano et al., 2020 [13]. A 19-20-year-old female received a combination of liraglutide and empagliflozin for 6 months. The treatment led to a marked decrease in body weight and a significant reduction in HbA1c levels. This case highlights the synergistic effects of combining GLP-1 receptor agonists with SGLT-2 inhibitors, showcasing improved insulin resistance and secretion. Senda et al., 2012 [10]. This report described a 25-year-old female who was administered liraglutide for one year. The patient's BMI decreased from 39.1 kg/m² to 35.7 kg/m², and HbA1c decreased from 12.6% to 6.1%. Additionally, hyperphagia and plasma ghrelin levels decreased, indicating a direct effect of the treatment on appetite control. Candler et al., 2020 [19]. An adolescent female was treated with liraglutide and empagliflozin for 6 months. The therapy was well tolerated, stabilized her weight, and normalized her HbA1c within the target range. This case underscores the efficacy of this combination therapy in managing diabetes and suggests a favorable safety profile, as shown in Table 1

Table 1: Summary of Patient Demographics and Clinical Outcomes for GLP-1 Receptor Agonist Treatment in PWS.

Case Reference	Patient Age	Gender	Treatment Regimen	Duration	Weight Loss	Change in HbA1c	Additional Outcomes
Ahmed et al., 2023	Adult	Male	Exenatide and Liraglutide	10 years	125 lbs	From 7.4% to 5.7%	Significant reduction in obesity-related complications
Sano et al., 2020	19-20 years	Female	Liraglutide and Empagliflozin	6 months	Marked decrease	Significant decrease	Improved insulin resistance and secretion
Senda et al., 2012	25 years	Female	Liraglutide	1 year	From BMI 39.1 kg/m ² to 35.7 kg/m ²	From 12.6% to 6.1%	Reduced hyperphagia, decreased plasma ghrelin levels
Candler et al., 2020	Adolescent	Female	Liraglutide and Empagliflozin	6 months	Stable weight	Normalized within target range	Well-tolerated treatment, sustained improvement

The summarized results demonstrate significant improvements in weight reduction, glycemic control, and appetite regulation, corroborating the therapeutic potential of GLP-1 receptor agonists for patients with Prader-Willi syndrome. Each case offers unique insights into different aspects of treatment outcomes, enriching understanding of how GLP-1 receptor agonists can be used optimally in the clinical management of PWS.

3.4 DISCUSSION

The case reports summarized in this review suggest that GLP-1 receptor agonists represent a promising therapeutic avenue in PWS management. The varied yet consistently positive outcomes highlight the potential for GLP-1 receptor agonists to address some of the most challenging aspects of PWS, particularly obesity, hyperphagia, and associated metabolic dysfunctions like diabetes mellitus. The case studies reveal significant benefits of GLP-1 receptor agonists in reducing body weight and improving glycemic control, which are critical concerns in PWS management. For instance, the long-term treatment (10 years) in the adult male reported by Ahmed et al. (2023, [18]) resulted in substantial weight loss (125 lbs) and an impressive reduction in HbA1c from 7.4% to 5.7%. This case illustrates the potential for sustained efficacy with GLP-1 receptor agonists and supports their role in long-term PWS management. Similarly, Sano et al. (2020) [13] reported cases using GLP-1 receptor agonists in combination with SGLT-2 inhibitors, which showed marked improvements in metabolic control. These combinations were well tolerated and led to significant improvements in insulin sensitivity and overall diabetic control, underscoring the potential synergistic benefits of using multiple pharmacological agents in PWS treatment protocols. A notable finding across the cases, particularly in the report by Senda et al. (2012) [10], is the effect of GLP-1 receptor agonists on hyperphagia. The reduction in appetite and food intake, evidenced by decreased plasma ghrelin levels, points to GLP-1 receptor agonists' ability to modulate neuroendocrine pathways involved in hunger signaling. This is particularly relevant for PWS patients, where uncontrolled appetite can lead to life-threatening obesity if not adequately managed. GLP-1 receptor agonists' ability to influence satiety suggests a dual therapeutic action: direct metabolic benefits and behavioral modification of food intake. While the therapeutic benefits of GLP-1 receptor agonists are clear, the long-term management of PWS using these treatments requires careful consideration. The extended duration of therapy reported by Ahmed et al. raises questions about the long-term safety and efficacy of chronic GLP-1 receptor agonist use [20]. Issues such as potential gastrointestinal side effects, the risk of pancreatitis, and the cost-effectiveness of these therapies in chronic conditions like PWS need thorough investigation [21]. Furthermore, the favorable safety profile observed in the adolescent case by Candler et al. provides preliminary support for using these treatments in younger populations. However, pediatric use of GLP-1 receptor agonists is not yet widely endorsed without further evidence, so additional studies are needed to fully establish safety parameters.

This review highlights the need for larger, controlled clinical trials to better evaluate the effectiveness and safety of GLP-1 receptor agonists in PWS. Given the complexity of PWS, multidisciplinary treatment approaches involving endocrinologists, dietitians, behavioral therapists, and pediatricians are essential to optimize outcomes [22]. Integrating GLP-1 receptor agonists into broader therapeutic frameworks could improve quality of life and health outcomes for individuals with PWS. Moreover, research into personalized medicine approaches, such as pharmacogenomics to predict response to GLP-1 receptor agonists, could improve treatment protocols by ensuring that patients most likely to benefit from these therapies are appropriately targeted. Lastly, developing non-invasive delivery mechanisms for GLP-1 receptor agonists could improve patient compliance and expand their use in younger populations, potentially transforming PWS management.

4. CONCLUSION

GLP-1 receptor agonists in managing PWS represent a significant advance in treating this complex genetic disorder. As evidenced by the case reports reviewed, these agents demonstrate substantial benefits in addressing critical symptoms of PWS such as hyperphagia, obesity, and metabolic dysfunctions like diabetes mellitus. Their potential to significantly improve weight management and glycemic control while reducing excessive appetite highlights the transformative impact they could have on treatment paradigms. However, larger, controlled studies are needed to establish long-term efficacy and safety, optimize dosing, and integrate these treatments into comprehensive care strategies. Continued research and clinical trials will be crucial to fully leverage GLP-1 receptor agonists to improve quality of life for individuals affected by PWS and potentially reshape the therapeutic landscape of this challenging condition.

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AUTHOR CONTRIBUTIONS

Not Applicable

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

ETHICS STATEMENT

This study did not require ethical approval.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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