Efficacy and Market Share of Glucagon-like Peptide 1 Receptor Agonists for Current Off-Label Uses: A Targeted Literature Review

Rachel Gamburg[1], Vishnu Bharadwaj Suresh[2], Ruihong Wang[1], and Coby Martin[3]

Introduction

- Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a class of injectable or oral medication that mimic the action of the naturally occurring incretin hormone, GLP-1.[1]
- GLP-1 RAs are currently FDA-approved for the treatment of type 2 diabetes mellitus (T2DM) and chronic weight management in adults with obesity, with selects agents also approved for adolescents and for reducing cardiovascular risk.[1]
- The clinical enthusiasm surrounding GLP-1 RAs has driven increased use in off-label indications, yet robust evidence supporting many of these emerging indications remains limited.

Objective

- The efficacy of GLP-1 RAs in off-label indications is not well known, nor are the prescription rates or cost-effectiveness. Therefore, a literature review was conducted to better understand off-label use, focusing on polycystic ovary syndrome (PCOS), Parkinson's Disease (PD), knee osteoarthritis (OA), addiction (alcohol, drug, and food), and Alzheimer's Disease (AD).

Methods

- Indications were selected based on exploratory research which identified therapeutic areas currently under investigation for treatment using GLP-1 RAs.
- A brief targeted literature review using PubMed and Embase databases was conducted from 2023 onwards and relevant studies were identified using search terms related to GLP-1 RAs, off-label indications, efficacy, cost-effectiveness, and off-label prescription.
- Two levels of screening (title/abstract and full text) and extraction was conducted, followed by summarization based on indications.
- Hand searches of ClinicalTrials.gov were performed to assess the volume of GLP-1 RA trials registered for each indication, complemented by bibliography searches of key review articles to capture studies not identified through database searching, including those published prior to 2023.

Results

- Database and hand searches identified 396 articles; 50 were included.
- A total of 141 clinical trials were identified (74 completed, 47 ongoing, 20 other), reflecting growing research into expanding GLP-1 RA indications (Figure 1).[2]
- **PCOS**: GLP-1 RAs consistently improve metabolic parameters and menstrual regularity in overweight/obese women with PCOS across meta-analyses and RCTs, but hormonal benefits are inconsistent, may not exceed diet or metformin alone, and evidence is largely limited to obese subpopulations (Figure 2).
- **PD**: Phase II PD trials showed motor improvements, but meta-analytic results were mixed, and the only Phase III trial was negative, leaving disease-modifying potential inconclusive (Figure 3).
- **AD**: One Phase II trial showed slowed cognitive decline and brain volume loss, and retrospective data suggest reduced AD risk, but shorter and Phase III trials were negative.[3-5] Due to minimal data, no graph was developed.
- **OA**: An RCT in obese knee OA patients and observational T2DM studies suggest GLP-1 RAs reduce symptom burden and slow cartilage loss, though evidence is limited to obese/diabetic populations with no OA-specific RCTs in non-obese patients (Figure 4).
- **Addiction:** A large meta-analysis and multiple retrospective cohorts show GLP-1 RAs reduce alcohol consumption, intoxication, cravings, and alcohol use disorder (AUD) hospitalizations, with semaglutide outperforming standard AUD medications in real-world data (Figure 5).
- Cost-effectiveness data are limited, though one study found tirzepatide and semaglutide cost-effective vs. usual care in knee OA and obesity, with tirzepatide offering the greatest value ($57,400/QALY).[6]
- Off-label GLP-1 RA prescribing is substantial: one study reported a 37.7% median rate; another found new prescriptions rose from 1.27 to 6.02 per 100 person-years (2016–2024) among patients with comorbid AUD and T2DM and/or obesity.[7,8]

Figure 1. GLP-1 RA Clinical Trials by Indication (ClinicalTrials.gov)

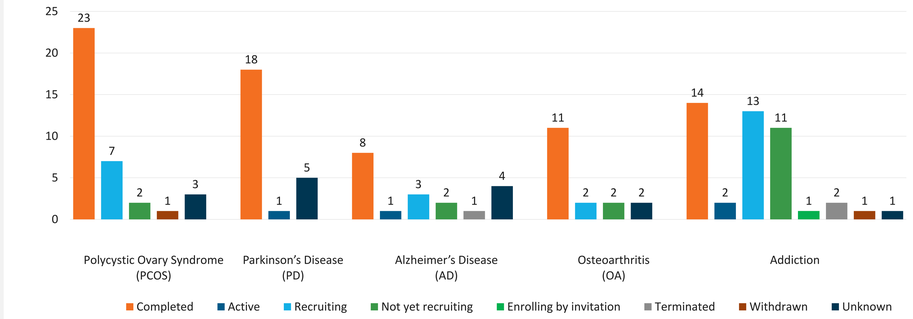


Figure 2. Clinical Study Outcomes for PCOS

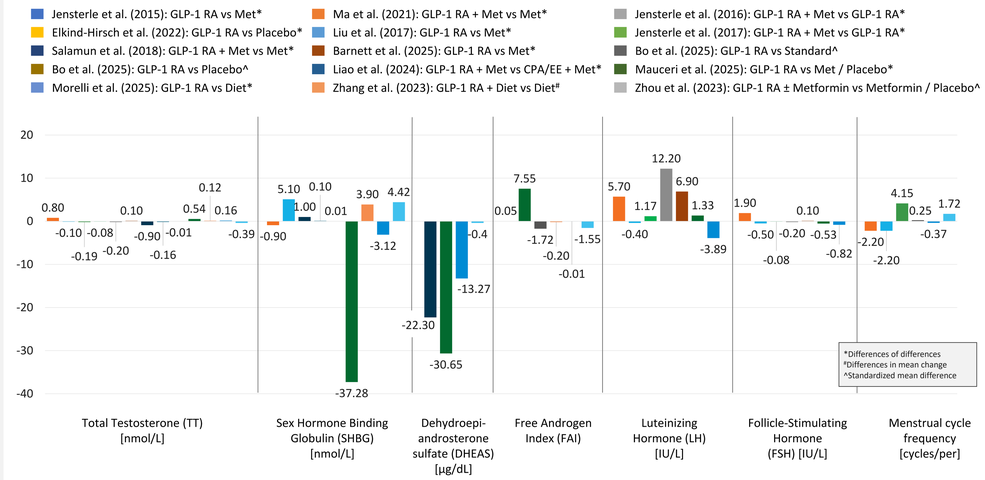
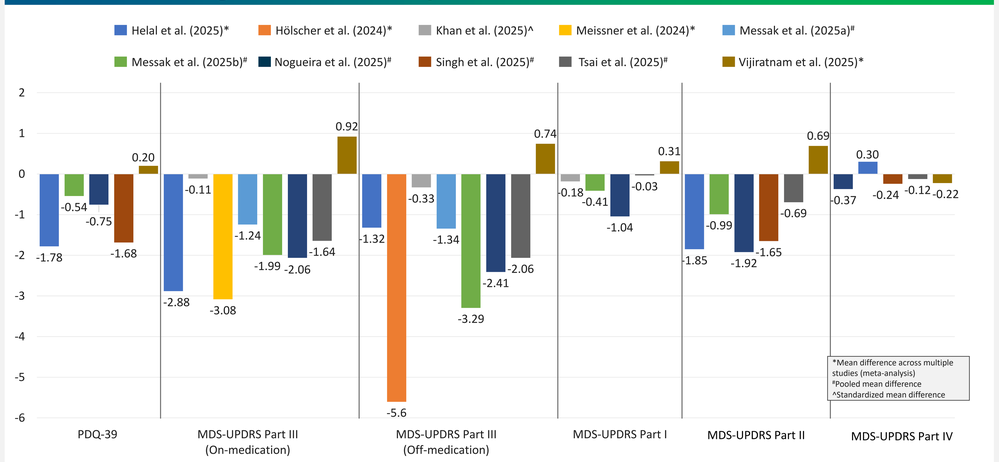
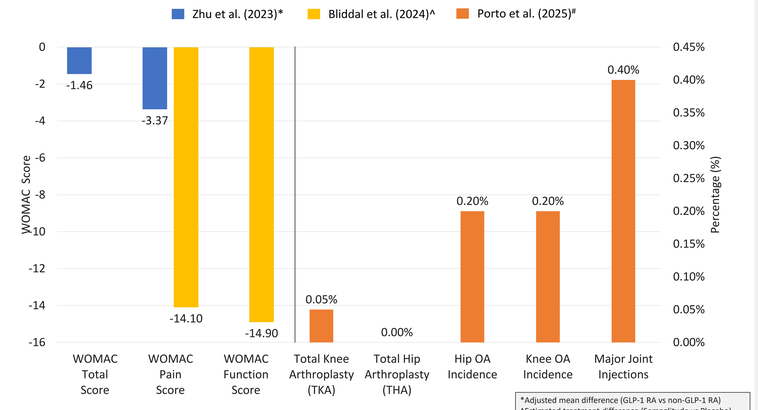


Figure 3. Clinical Study Outcomes for Parkinson's Disease



MDS-UPDRS: Movement Disorder Society - Unified Parkinson's Disease Rating Scale

Figure 4. Clinical Study Outcomes for Osteoarthritis



WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Figure 5. Clinical Study Outcomes for Addiction

AUDIT: Alcohol Use Disorders Identification Test

Discussion & Conclusion

- It is important to note that, for studies found in this review, most evaluated patients with indications comorbid with obesity or T2DM.
- Although successes are more often discussed, several clinical trials have failed, including EVOKE and EVOKE+ for semaglutide in AD, which did not meet their primary endpoints.[6]
- The landscape of GLP-1 RAs is constantly evolving, with new policies impacting market access, such as the change in 2025 which removed Medicare and Medicaid coverage of anti-obesity drugs like GLP-1 RAs applied in 2026.[7]
- GLP-1 RAs show promising but mixed efficacy across off-label indications, while side effects like gastrointestinal distress were consistently observed and long-term safety remains uncertain.
- Due to high off-label uptake and variable market share across communities, monitoring and investigation of availability are important for GLP-1 RAs to ensure access for patients with diseases that may benefit most from GLP-1 RA treatment.

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