Off-Label Use of and Adherence to GLP-1RAs as Adjunct Therapy in Type 1 Diabetes: A Comparative Analysis Versus Metformin

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Harry Gyimah Gyamfi MS[1], Oliver Titus MS[1] , Robert Valuck PhD, RPh[1] , Heather Anderson PhD[1]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, USA

Background

- Approximately **38%** of patients with type 1 diabetes (T1D) are obese[1], complicating glycemic control.
- This has led to increased off-label use of GLP-1 receptor agonists (GLP-1RAs) in T1D to support both weight management and glucose control[2].
- In contrast, metformin is a commonly used and established adjunct to insulin in T1D.
- Nevertheless, in type 2 diabetes (T2D) adherence to GLP-1RA is a serious concern leading to **36%** discontinuation rate in 12 months[2].
- Despite greater unmet glycemic needs in T1D compared to T2D, real-world adherence to off-label use of GLP-1RAs remains poorly characterized in T1D.

Objectives

Primary objective: To compare adherence of GLP-1RAs versus metformin in T1D and examine factors influencing adherence using real world claims data.

Secondary Objective: To examine factors associated with GLP-1RA adherence in T1D, including endocrinologist visit frequency and GLP-1RA switching patterns.

Methods

Study Design:

- Retrospective cohort study using the IQVIA PharMetrics® Plus for Academics claims data.
- **Study Cohort**

1) Patients with type 1 diabetes (T1D), aged ≥14 years, who initiated either a GLP-1RA or metformin from January 1, 2017, to May 31, 2024
2) At least 12 months of continuous enrolment prior to treatment (baseline period)
3) Minimum of 3 months of follow-up after treatment initiation

- **Primary Outcome:**

Adherence, defined as proportion of days covered (PDC) ≥**80%**[3] during follow-up

- **Main Exposure:**

Adjunct GLP-1RA or metformin therapy was defined as a prescription fill for either agent among patients with a documented diagnosis of type 1 diabetes.

- **Exclusion Criteria:**

1) Type 2 diabetes diagnosis (ICD-10: E11)
2) Prior use of GLP-1RA or metformin within 180 days before index date
3) <3 months of follow-up after treatment initiation
4) Discontinuation, switching between GLP-1RAs and metformin, or DKA event during follow-up.

Statistical Analysis:

1) Inverse probability of treatment weighting (IPTW) based on propensity scores was used to balance baseline covariates.
2) Doubly robust approach combining IPTW with covariate-adjusted modified Poisson regression using robust standard errors to estimate risk ratios.

- **Sensitivity Analyses:** Alternative PDC thresholds (≥85%, ≥90%) and E-values were used to assess robustness.
- **Key Variabless:** Switching (change from index GLP-1RA to another GLP-1RA), Endocrinologist visits (number of distinct endocrinology visits during follow up).
- **Covariates for IPTW and Model**: age, sex, patient region, insurance plan type, insurance type, obesity status, Charlson comorbidity index and history of hospitalization prior to index

Results

Table 1: Baseline demographics and cohort characteristics in Unweighted group

Variable	GLP-1RA (N = 284[1])	Metformin (N = 1010[1])	p-value[2]
Age	58(14%)	55(18%)	0.01
Females	166(58%)	502(50%)	0.009
Insurance			0.2
Commercial	115 (40%)	454 (45%)	
Medicare/Medicaid	169 (60%)	550(54%)	
Other	0 (0%)	6 (0.6%)	
Obesity	151 (53%)	373 (37%)	<0.001
CCI[3]	3.55(2.73)	4.79(2.55)	<0.001

[1] Mean (SD); n / N (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test [3]CCI= Charlson Comorbodity Index

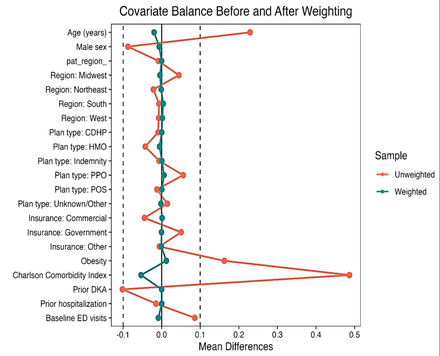

Figure 1: Covariate Balance Before and After Weighting. *Standardized mean differences (SMDs) are shown before and after inverse probability of treatment weighting Dashed lines at ±0.10 indicate acceptable balance.*

Adherence to Off-label GLP-1RAs Vs Metformin In T1D

- In the unadjusted cohort, a lower proportion of GLP-1RA users (59.4%) were adherent compared to metformin users (83%).
- In the doubly robust model, T1D GLP-1RA users had a **28% lower risk** (95% CI: 28%-35%, p<0.001) of being adherent as compared to metformin users.

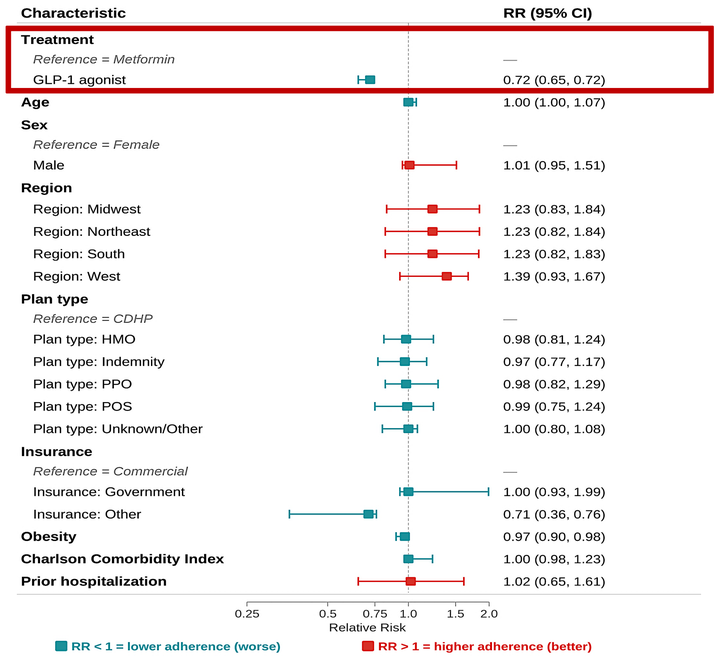

Figure 2: Forest plot of adjusted risk ratios for adherence among patients with type 1 diabetes. *Risk ratios (RRs) and 95% confidence intervals were estimated using a doubly robust approach combining inverse probability of treatment weighting (IPTW) with covariate-adjusted modified Poisson regression and robust standard errors. The reference group is metformin.*

Results II

Adherence Patterns Among GLP-1RA Users in T1D

- **20%** of patients (n = 57) switched GLP-1RA from their index GLP-1RA to another . The most common GLP-1RAs switched to were:
  a. Semaglutide (46%, n = 26) b. Dulaglutide (23%, n = 13) c.Tirzepatide (16%, n = 9)
- Each **additional GLP-1RA switch** was associated with an average **42% lower likelihood** of adherence (RR = 0.58; 95% CI 0.39-0.81; p = 0.003).
- Probability of adherence **declined after five endocrinologist visits**; among patients who switched GLP-1RA therapy, adherence decreased by **21%** (95% CI: 15%- 43%).
- No significant difference in adherence was observed between daily and weekly GLP-1RA regimens(p>0.5).

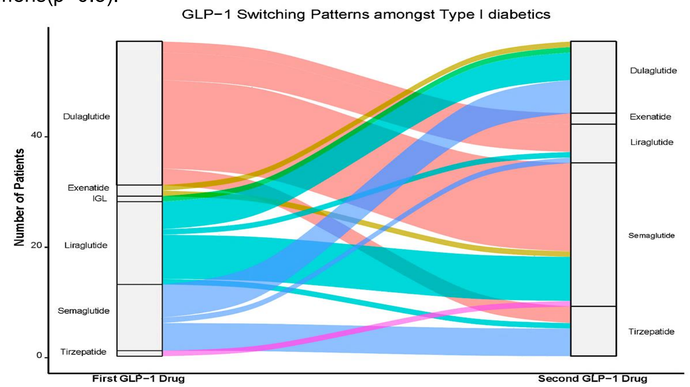

Figure 2: Sankey diagram of switching pattern from initial prescribed GLP-1RA to another GLP-1RA amongst T1D patients. *Most patients on dulaglutide(red color) switched to a second GLP-1 with Tirzepatide(pink pattern) having the least switch.*

Sensitivity Analysis: Results were consistent across PDC thresholds (≥85%, ≥90%), with lower adherence among GLP-1RA users. The E-value (2.12) indicates moderate robustness to unmeasured confounding.

Conclusion

- **GLP-1RA users with type 1 diabetes were less likely to be adherent** compared to those on metformin, despite increasing off-label use.
- **Prescribers should assess adherence risk** before initiating GLP-1RA therapy, especially in patients with a prior history of non-adherence in T1D.
- **Switching between GLP-1RA agents was common** and associated with lower adherence.
- **Adherence declined after the first five endocrinologist visits**, indicating that the early treatment window is critical for reinforcing adherence.
- **Interventions such as counselling on side effects and treatment goals** during the **first five visits** may improve long-term adherence and clinical outcomes of GLP-RAs in T1D.

Limitations

- Clinical and patient-level factors influencing non-adherence (e.g., side effects, patient preferences) could not be captured due to limitations of claims data
- The use of PDC as a proxy for adherence may introduce measurement bias, since medication fills do not guarantee actual use.

References

1. Xu, Y., et al., *Trends in obesity and glucagon-like peptide-1 receptor agonist prescriptions in type 1 diabetes in the United States.* Diabetes Obes Metab, 2025
2. Do, D., et al., *GLP-1 Receptor Agonist Discontinuation Among Patients With Obesity and/or Type 2 Diabetes.* JAMA Network Open, 2024. **7**(5): p. e2413172-e2413172
3. Prieto-Merino et al. Estimating proportion of days covered (PDC) using real-world online medicine suppliers' datasets. J Pharm Policy Pract. 2021 Dec 29;14(1):113. doi: 10.1186/s40545-021-00385-w. PMID: 34965882; PMCID: PMC8715592.