Exposure-Adjusted Safety and Efficacy of GLP-I and GLP-1 / GIP Receptor Agonists Compared to Non-GLP-I for Weight Management and Type 2 Diabetes: Based on FDA Medical and Statistical Reports of 34,280 Safety and 36,312 Efficacy Subjects

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Introduction

Over the past decade, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GLP-1/GIP receptor agonists have fundamentally reshaped weight management and are now being evaluated for diverse indications such as diabetes prevention, liver disease, osteoarthritis, and polycystic ovarian syndrome. While early animal studies raised concerns about pancreatitis, pancreatic cancer, and thyroid cancer, meta-analyses of human trials have shown no significant increase in these adverse events, supporting their favorable efficacy and safety profile. Prior meta-analyses, however, have been limited by focusing only on published trials, including drugs not FDA-approved, or failing to contextualize GLP-1 agents against older medications such as sibutramine and naltrexone/bupropion. To address these gaps, we reviewed FDA Medical and Statistical Reports for 14 drugs across 46 pivotal trials, analyzing safety in 34,280 participants and efficacy in 36,312 participants, using patient-exposure year normalization to provide a more accurate assessment of comparative safety and efficacy.

Methods

We searched the FDA database through September 2025 (www.accessdata.fda.gov/scripts/cder/daf/index) for all approved non-GLP-1 medications for obesity (orlistat, phentermine/topiramate, maltrexone/bupropion, sibutramine), GLP-1 receptor agonists (GLP-1 RAs) for weight management (liraglutide, semaglutide), GLP-1 RAs for treatment of type 2 diabetes (subcutaneous semaglutide, oral semaglutide, lixisenatide, albiglutide, rapid-acting exenatide), and GLP-1 / GIP RAs approved for weight management and type 2 diabetes (tirzepatide).

Inclusion Criteria: Availability of both drug and placebo groups in randomized clinical trials, safety data for trial participants of varying severity, approved doses, and discontinued medications

Exclusion Criteria: Extension trials, cardiovascular outcomes trials (CVOTs).

We assessed the safety and efficacy of fourteen medications that met the criteria, encompassing a total of 36,312 participants.

Mortality refers to deaths; deaths in the lead-in period were excluded.

Severe Adverse Events (SAE): According to the definition given by most FDA programmes, severe adverse events are described as life-threatening conditions, permanent disability, or hospitalization, as well as events requiring intervention to prevent these outcomes. The terms “SAE” and “morbidity” are used interchangeably.

Patient Exposure Years (PEY): PEY was calculated to assess treatment exposure duration. When PEY was not directly available, we calculated it by dividing exposure weeks by 52, multiplying by the number of participants, and summing the results. Mortality rates were determined by dividing the number of deaths by total PEY for each drug category and multiplying by 100,000. Same method was used to calculate morbidity rates.

We extracted mean age, percentage female, study duration, baseline and end-of-study weights, incidence of serious adverse events (SAEs), deaths, and patient-exposure years (PEY).

We calculated mortality and morbidity rate ratios (RRs) with 95% confidence intervals using person-years of exposure, applying continuity corrections for zero-event groups and log-transformed RRs for statistical testing. Treatment response was defined as weight change from baseline, with group means and standard deviations pooled across arms; when only standard errors were reported, we converted them to SDs. Effect sizes were calculated using Cohen’s d to compare weight change between treatment and placebo. Finally, we cross-checked all 45 FDA-reviewed trials against corresponding publications to evaluate potential under-reporting or reporting bias.

Results

We evaluated the safety and efficacy of fourteen medications across forty-six trials. The mean age across all trials was 48.4 years, with 72.1% of participants were female. The median study duration was 52 weeks, with a range of 16 to 104 weeks. As anticipated, the efficacy database (N = 36,312) was larger than the safety database (N = 34,280), as the latter included only participants who had received at least one dose of study medication.

Although the greatest weight reduction was observed in GLP-1 / GIP RAs approved for weight management, we did not consider any of the available statistical tests to be valid for establishing significance. As anticipated, the effect size was very large for patients assigned to the specifically approved weight loss agents liraglutide (0.6) and tirzepatide (1.1). Surprisingly, naltrexone HCL / bupropion HCL had similar effect sizes to liraglutide (average 0.6) (see Table 1).

Table 1: Efficacy of Body Weight Reduction for Trial Participants in non-GLP-1, GLP-1 Receptor Agonists, and GLP-1 / GIP Receptor Agonists for Weight Management Trials and GLP-1 Receptor Agonists and GLP-1 / GIP Receptor Agonists for Type 2 Diabetes Trials

Medication	Trial ID	Average Baseline Weight, kg (SD)	Average % Change from Baseline: Placebo ± SD	Average % Change from Baseline: Drug ± SD	Effect Size
Section A: non-GLP-1 Medications Approved for Weight Management					
i. Orlistat - OTC	*XM14143 / XM14161*	99.3 (14.4)	-1.8	-4.5	…
	XM17247	72.8 (6.8)	-2.6	-4.2	…
ii. Orlistat - Prescription	-	96.5	*n/a*	*n/a*	…
iii. PhentermineT opiramate	*OB-302, OB-303*	107 (20.1)	-1.7	-8.0	…
	OB-305	101.7 (18.7)	-2.5	-10.9	…
iv. Naltrexone HCL / Bupropion HCL	*NB-301*	99.9 (15)	-1.3 ± 7.2	-5.6 ± 7.2	0.6
	NB-302	101 (15.3)	-5.1 ± 8.5	-9.3 ± 9.7	0.5
	NB-303	100.2 (16.5)	-1.9 ± 6.7	-6.5 ± 6.3	0.7
v. Sibutramine	*SB1049*	96.7	0.9	-5.2	…
	SB3059	89.1	-5.6	-7.8	…
Total	**5 Medications**	**97.3**	**-2.3**	**-6.7**	
Section B: GLP-1 Medications Approved for Weight Management					
i. Liraglutide	*NN8022-1839*	106.3 (21.4)	-2.6	-8.0	…
	NN8022-1922	106.1 (21.5)	-2.0	-5.3	…
	NN8022-1923	99.5 (21)	-0.1 ± 9.1	-6.1 ± 9.6	0.6
ii. Semaglutide	*STEP 1*	105.3 (21.9)	-2.4	-14.9	…
	STEP 2	99.8 (21.5)	-3.4	-9.6	…
	STEP 3	105.8 (22.8)	-5.7	-15.97	…
	STEP 4	96.1 (22.6)	6.9	-7.9	…
Total	**2 Medications**	**104.1 (22)**	**-1.3**	**-9.7**	
Section C: GLP-1 Receptor Agonist Medications Approved for Type 2 Diabetes (T2D)					
i. SC Semaglutide	*Sustain 1*	91.2	-1.1	-4.4	…
	Sustain 5	91.7 (21)	0.5	-6.5	…
ii. Semaglutide	*Pioneer 1*	88.2 (22.1)	-1.6	-2.8	…
	Pioneer 4	93 (20.4)	-0.6	-4.7	…
	Pioneer 5	90.9 (17.6)	-1.0	-3.8	…
	Pioneer 8	85.9 (21.9)	-0.6	-3.0	…
iii. Lixisenide†	-	83.6	-0.7	-1.4	…
iv. Albiglutide††	-	93.5 (20.3)	-0.4	-0.5	…
v. Exenatide	*112/113/115*	98.5	-0.6	-1.6	…
	GWBJ	85.9	-1.7	-3.4	…
Total	**5 Medications**	**90.2 (4.4)**	**-0.8**	**-3.2**	
Section D: GLP-1 / GIP Receptor Agonist Medication Approved for Type 2 Diabetes (T2D) and Weight Management					
i. Tirzepatide (WM)	*Surmount 1*	105.4 (22.7)	-3.1 ± 15.2	-18.5 ± 12.1	1.1
	Surmount 2	100.7 (21.1)	-3.2 ± 8.9	-13.7 ± 9.8	1.1
ii. Tirzepatide (T2D)	*Surpass 1*	86 (19.8)	-1.2	-8.1	…
	Surpass 5	95.2 (21.6)	1.7	-7.9	…
Total	**2 Medications**	**101.2 (22.8)**	**-1.5**	**-12.1**	

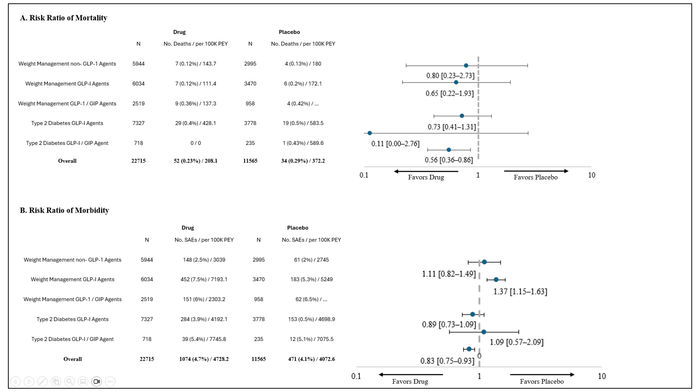
… Standard deviations were for change from baseline not available, therefore, effect size could not be calculated

† Studies included cohorts for monotherapy, add on to metformin, add on to SU or SU+Met, add on to Pio or Pio+Met, add on to Bl or Bl+Met, add on to IG+Met or IG+Met+T2D, add on to Bl or Bl+SU, add on to Met or Met+SU

†† Studies included cohorts for monotherapy, add on to metformin, add on to pioglitazone ± metformin, add on to pioglitazone ± metformin, and add on to metformin and sulfonylurea

The mortality rates were lower in the medication groups compared to placebo groups. This pattern is common in clinical trials, as both the total duration of exposure and the number of participants are typically higher in the treatment groups. However, this can result in elevated raw event rates that may not accurately reflect the true safety profiles of the investigational agents. Therefore, we adjusted mortality and morbidity rates based on patient-exposure years (PEY), as described in Figure 1.

Figure 1: Risk Ratios and 95% Confidence Intervals for Mortality and Morbidity Among Patients Treated With non-GLP-1, GLP-1, and GLP-1/GIP Agents Compared to Placebo



Conclusion

Our analysis shows that GLP-1 RAs approved for weight management represent a substantial therapeutic advancement over both traditional weight management agents and GLP-1 RAs studied in type 2 diabetes (T2D), with GLP-1/GIP dual agonists emerging as highly efficacious. The use of FDA archives offers a unique perspective that complements both published meta-analyses and real-world data. By integrating these sources, applying exposure-adjusted denominators, and situating safety outcomes within the broader context of pharmacotherapy, we provide a framework for evaluating efficacy and safety across indications. Moving forward, it is crucial that both peer-reviewed publications and FDA regulatory documents consistently report patient-exposure years, standard deviations, errors, and confidence intervals to enable a comprehensive assessment of therapeutic benefit and risk. These data provide essential insights for physicians, clinicians, and researchers, equipping them with the evidence needed to make informed decisions and to contextualize emerging therapies, such as GLP-1 and GLP-1/GIP agents, as they continue to reshape the management of obesity and its related diseases.

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