dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
YEAR 2023
VOL 31, Issue 4
www.dtb.navarra.es
@DTBNavarre.es

Bol Inf Farmacoter Navar. 2023;31 (4):1-19
https://doi.org/10.54095/BITN20233104EN

Glucagon-like peptide 1 receptor agonists (GLP1a) and the problem of obesity

INTRODUCTION The prevalence of obesity has tripled over the past 40 years. Several glucagon-like peptide 1 receptor agonists (GLP1a) have been authorised for weight loss recently. OBJECTIVE To analyse the evidence supporting the use of GLP1a for overweight and obesity in non-diabetic adult patients. To discuss the role thereof in the fight against the obesity epidemic. Methods. The pivotal clinical trials of liraglutide, semaglutide and tirzepatide in non-diabetic adult patients published up until April 2024 were examined. Trials studying the effects of suspending treatment and one trial in patients with established cardiovascular disease were also analysed. RESULTS GLP1a provoke weight loss while treatment remains ongoing. In secondary prevention, semaglutide reduces the risk of cardiovascular events to a modest extent. The use of surrogate outcomes, the proportion of withdrawals and problems of external validity limit the relevance of these findings.. Gastrointestinal adverse events are common and the incidence of serious events is notable. CONCLUSIONS The role of GLP1a in therapeutic medicine remains to be clearly defined, therefore the prescription thereof should be restricted to the sub-groups that will achieve the greatest benefit. Accessibility to lifestyle interventions should be ensured. The solution to the obesity epidemic requires political intervention regarding the social factors that promote it.

SANTI ARANA BALLESTAR
Family and Community Medicine resident
Centro de Salud Parque Goya (Zaragoza)

CRUZ BARTOLOMÉ MORENO
Family and Community Medicine Specialist
Centro de Salud Parque Goya (Zaragoza)
Family and Community Care Teaching Unit. Sector Zaragoza I

index

Introduction

Overweight and obesity

According to the World Health Organisation, overweight and obesity are defined in terms of the body mass index (BMI): overweight ≥25 kg/m^2 and obesity ≥30 kg/m.[2 1]

The prevalence of overweight and obesity in Navarra is 34% and 13%, respectively, with these values being slightly lower than those for Spain as a whole.[2] The severity of obesity can be categorised as grade I (BMI 30–35 kg/m^2), grade II (BMI 35-40 kg/m^2) or grade III (severe or morbid, BMI ≥40 kg/m^2).[1,3] In the Spanish population aged between 25 and 64 years, 16.5% of people can be categorised as grade I, 3.6% as grade II and 1.6% as grade III[3].

Overweight and obesity are the result of a positive energy balance, which results from ingesting more calories than are used[4]. This situation can be explained by the problematic influence of an obesogenic environment on biological, psychological, social and economic vulnerabilities[5]. This contextual perspective explains why the prevalence of obesity has tripled over the past four decades.

Excess adiposity has been associated with increased morbidity (cardiovascular diseases, cancer, diabetes, etc.) and a worse quality of life (functional capacity, perceived health)[4]. Obesity increases mortality due to both its association with the above-mentioned comorbidities and independently. In contrast, despite its association with comorbidities, the mortality of people with overweight appears to be similar to that of people with a normal weight[6].

This, and other similar findings, suggest that BMI is an inaccurate tool for discriminating the really harmful adiposity and identifying people most at risk. Its predictive value for estimating body fat, bone mass and lean mass of an individual is very limited[7]. In addition, other factors, such as body-fat distribution or weight evolution during a person's lifetime, may affect the relationship thereof with morbidity and mortality[6]. Consequently, the isolated use of BMI as a clinical-evaluation tool is inadequate[6,7], and the current categories (normal weight, overweight, obesity) may perhaps need to be redefined to reflect its actual relationship with morbidity and mortality[6].

Treatment of obesity

The treatment of obesity is mainly based around lifestyle-modifying programs. For example, motivational interviews and health education are used to try to promote adherence to a healthy, low-calorie diet and increase physical activity[8].

Indeed, intensive lifestyle interventions may result in losses of up to 10% of the initial body weight and improvements in various parameters (such as blood pressure and cholesterolaemia), although the results in terms of cardiovascular morbidity and mortality are inconclusive. However, the proportion of patients who manage to access these high-intensity interventions is limited and, despite initial weight losses, it often proves difficult to maintain the target weight[9].

If the lifestyle intervention does not achieve a weight loss of at least 5% of the initial weight, for people with a BMI ≥30 kg/m^2 or 27–29.9 kg/m^2 with comorbidities, pharmacological treatment is recommended[8]. Various drugs with different mechanisms of action and indications cause weight loss (antiepileptics, antidepressants, antidiabetics, etc.). A recently published pharmacotherapeutic bulletin analyses these options[10]. It should be noted that, over the past few decades, at least twenty five drugs indicated for the treatment of obesity (sibutramine, rimonabant,dexfenfluramine,etc.)havebeen withdrawn, and some of those that are still authorised appear to present similar problems (neurological, psychiatric, cardiovascular and gastrointestinal adverse events)[11].

Bariatric surgery is reserved for patients with a BMI ≥ 40 kg/m^2 or ≥35 kg/m^2 with severe comorbidities that do not respond to the previous interventions. Although follow-up in trials was limited to 1–2 years[12], surgery is considered to be the only effective intervention for long-term

weight loss[8]. Although the effect of surgery on morbidity and mortality was not studied in trials, observational studies have suggested a reduction in all-cause mortality[13].

As of the date this bulletin was drafted (june 2024), three drugs are approved for the treatment of obesity in Spain: orlistat, liraglutide (Saxenda®) and semaglutide (Wegovy®). The former is a gastric and pancreatic lipase inhibitor and the latter two are glucagon-like peptide 1 receptor agonists (GLP1a).

Orlistat increases faecal fat excretion[10], and has a modest and transitory effect on weight. In trials, patients lost around 3.5 kg versus placebo in 12–24 months, although there was no evidence for long-term efficacy. Gastrointestinal disorders were common, and liver damage, hyperoxaluria and bone fractures in adolescents have also been reported. In addition, it alters the gastrointestinal absorption of numerous nutrients (liposoluble vitamins A, D, E and K) and reduces the efficacy of several drugs (thyroid hormones, antiepileptics and contraceptives)[14].

GLP1 receptor agonists (GLP1a)

GLP1a slow gastric emptying and reduce appetite. The first drug from this family—exenatide—was approved in 2005 for the treatment of type 2 diabetes. According to a meta-analysis of 8 clinical trials, in this indication GLP1a reduce cardiovascular events, all-cause mortality and the worsening of renal function[15].

In 2015, liraglutide (Saxenda®) was the first GLP1a to be authorised by the European Medicines Agency (EMA) for use in the treatment of overweight and obesity in non-diabetic patients. Semaglutide (Wegovy®) was authorised for the same indication in 2022 and tirzepatide (Mounjaro®) in 2023. In Spain, Saxenda® and Wegovy® are not funded.

There have been severe supply problems for these active substances in the past few months, especially their presentations for type 2 diabetes (Ozempic®, semaglutide; Victoza®, liraglutide; Trulicity®, dulaglutide), due to their off-label use for weight loss. Indeed the Spanish Agency for Medicines and Medical Devices (AEMPS) has published several recommendations in order to ensure the supply for diabetic patients[16].

According to the latest update of the list of medicines to be avoided in the journal *Prescrire* (february 2024), no medicine is able to induce lasting weight loss without causing harm[14]. In contrast, in late 2023, the journal Science awarded its *Breakthrough of the Year* prize to GLP1a as they have transformed "medicine, popular culture and world stock markets in an electrifying manner"[17].

Analysis of the evidence for GLP1a in non-diabetic patients

This review includes phase-3 clinical trials evaluating the efficacy of liraglutide (SCALE[18]), semaglutide (STEP-1[19], STEP-3[20], STEP-5[21]) and tirzepatide (SURMOUNT-3[22]) versus placebo for weight loss. Two studies concerning the consequences of withdrawing treatment once weight loss has been induced (STEP-4[23], with semaglutide; SURMOUNT-4[24], with tirzepatide), have also been included.

In addition, the STEP-8[25] trial compares the efficacy of liraglutide versus semaglutide in weight loss. A final study, namely the SELECT trial[26], evaluated the efficacy of semaglutide versus placebo in the secondary prevention of cardiovascular disease. The main characteristics and results of these trials, differentiating on the basis of the studied outcome, are presented below.

Table 1 lists the trial type, masking, outcomes, interventions compared and follow-up time. Table 2 provides the composition of the groups included in the trial: calculated sample size, size finally recruited and number of patients who abandoned treatment during the trial.

Table 3 provides the characteristics of the population finally included in each trial. Any additional interventions to treatment are indicated, and potential limitations of the studies are discussed. Table 4 summarises the most relevant outcomes for each trial. Table 5 lists the most important adverse events by frequency and severity.

Table 1. Studies included in this article: triple blind, quality, outcome variable, groups and follow-up time.

VANCOUVER CITATION	APA CITATION	STUDY NAME	CLINICAL TRIAL IDENTIFICATION NUMBER	TYPE OF STUDY	RANDOM SEQUENCE	BLIND PARTICIPANT	BLIND OBSERVER	BLIND ANALYSIS	QUALITY ACCORDING TO TYPE OF STUDY*	OUTCOME	GROUPS	FOLLOW-UP
Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892. PMID: 26132939.	Pi-Sunyer, 2015	SCALE, 2015	NCT01272219	Phase 3 RCT	Yeah	Yeah	Yeah	No	High	Surrogate: weight change, ≥5% weight loss, ≥10% weight loss	Liraglutide *vs.* Placebo	56 weeks
Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP-1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.	Wilding, 2021	STEP-1, 2021	NCT03548935	Phase 3 RCT	Yeah	Yeah	Yeah	Yeah	High	Surrogate: weight loss ≥5%, weight % change	Semaglutide *vs.* Placebo	68 weeks
Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP-3 Randomized Clinical Trial. JAMA. 2021;325(14):1403–1413. doi:10.1001/jama.2021.1831	Wadden, 2021	STEP-3, 2021	NCT03611582	Phase 3 RCT	Yeah	Yeah	Yeah	Yeah	High	Surrogate: weight loss ≥5%, weight % change	Semaglutide *vs.* Placebo	68 weeks
Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, Wharton S; STEP-5 Study Group. Two-year effects of semaglutide in adults with overweight or obesity: the STEP-5 trial. Nat Med. 2022 Oct;28(10):2083-2091. doi: 10.1038/s41591-022-02026-4. Epub 2022 Oct 10. PMID: 36216945; PMCID: PMC9556320.	Garvey, 2022	STEP-5, 2022	NCT03693430	Phase 3 RCT	Yeah	Yeah	Yeah	Yeah	High	Surrogate: weight loss ≥5%, weight % change	Semaglutide *vs.* Placebo	104 weeks
Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, Halpern B, Zhang S, Chen J, Bunck MC, Ahmad NN, Forrester T. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023 Nov;29(11):2909-2918. doi: 10.1038/s41591-023-02597-w. Epub 2023 Oct 15. PMID: 37840095; PMCID: PMC10667099.	Wadden, 2023	SURMOUNT-3, 2023	NCT04657016	Phase 3 RCT	Yeah	Yeah	Yeah	No	High	Surrogate: weight loss ≥5%, weight % change	Tirzepatide *vs.* Placebo	72 weeks
WEIGHT RECOVERY TRIALS												
Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP-4 Investigators. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP-4 Randomized Clinical Trial. JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. PMID: 33755728; PMCID: PMC7988425.	Rubino, 2021	STEP-4, 2021	NCT03548987	Phase 3a RCT	Yeah	Yeah	Yeah	Yeah	High	Surrogate: % weight change	Semaglutide *vs.* Placebo	68 weeks
Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, Ahmad NN, Zhang S, Liao R, Bunck MC, Jouravskaya I, Murphy MA; SURMOUNT-4 Investigators. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA. 2024 Jan 2;331(1):38-48. doi: 10.1001/jama.2023.24945. PMID: 38078870; PMCID: PMC10714284.	Aronne, 2024	SURMOUNT-4, 2024	NCT04660643	Phase 3 RCT	Yeah	Yeah	Yeah	No	High	Surrogate: % weight change	Tirzepatide *vs.* Placebo	88 weeks
HEAD TO HEAD WEIGHT TRIALS												
Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP-8 Randomized Clinical Trial. JAMA. 2022;327(2):138–150. doi:10.1001/jama.2021.23619	Rubino, 2022	STEP-8, 2022	NCT04074161	Phase 3b RCT	Yeah	Yeah	Yeah	Yeah	High	Surrogate: % weight change	Semaglutide *vs.* Liraglutide *vs.* Placebo	68 weeks
CLINICAL OUTCOME TRIALS												
Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221-2232.	Lincoff, 2023	SELECT, 2023	NCT03574597	Phase 3 RCT: superiority trial	Yeah	Yeah	Yeah	Yeah	High	Combined: death + AMI + stroke	Semaglutide *vs.* Placebo	137 weeks

(*) They are considered high quality due to the type of study: Randomized clinical trial

Tabla 2. Description of the number of patients who start and finish in each study and the number and causes of non-completion.

ARTICLE	SAMPLE SIZE NECESSARY TO MAKE AN INFERENCE (n)	TREATMENT GROUP (GT)							CONTROL GROUP (GC)							DIFFERENCE PATIENTS WHO COMPLETE TREATMENT IN GI AND GC
		They start treatment	Complete treatment finished		They do not complete treatment: they discontinue		Causes	Losses	They start treatment	Complete treatment finished		They do not complete treatment: they discontinue		Causes	Losses	
		(n)	(n)	(%)	(n)	(%)			(n)	(n)	(%)	(n)	(%)			
SCALE, 2015	3600(2:1; 2400 lira and 1200 placebo)	2487	1789	71.9	698	28	Adverse events: 246 (10%), withdrawals of consent: 286 (12%) and other causes: 166 (7%)	496 (20%)	1244	678	64	194	16	Adverse events: 47 (3.8%) and other causes: 147 (11.8%)	332 (27%)	8
STEP-1, 2021	1950 (2:1; 1300 sema and 650 placebo)	1306	1083	82.92	223	17	Adverse events: 91 (7%), consent withdrawal 9 (1%), other reasons: 56 (5%) and missing information for 67 (5%)	66 (5%)	655	499	73	78	7	Adverse events: 5 (0.8%) and other reasons: 41 (6.3%). There is no data for 32 (4.89%)	46 (7%)	10
STEP-3, 2021	600 (2:1; 400 sema and 200 placebo)	407	336	83	40	10	Adverse events: 24 (6%) and other reasons: 16 (4%)	31 (8%)	204	165	81	26	13	Adverse events: 6 (%) and others: 20 (10%)	Losses: 7 (3%), withdrew consent: 3 (2%) and withdrew from the study: 1 (1%), no information available: 2 (1%)	2
STEP-5, 2022	304 (1:1; 152 in each group)	152	132	87	20	13	Adverse events: 10 (7%) and others: 10 (7%)	4 (3%)	152	111	73	41	39	Adverse events: 7 (5%) and others: 34 (22%)	18 (12%)	14
SURMOUNT-3, 2023	(1:1) 600: 300 in each group	287	226	78.7	61	21	Adverse events 33 (11.5%)	32 (11%)	292	203	70	89	31	Adverse events 7 (2%)	70 (24%)	8.7
WEIGHT RECOVERY TRIALS																
STEP-4, 2021	750 (2:1; 500 plus 250)	535	504	94	24	5	Adverse events: 11 (2%) and others: 13 (2%)	7 (1%)	268	237	88	23	9	Adverse events 6 (2%) and others 23 (9%)	8 (3%)	6
SURMOUNT-4, 2024	(1:1) 600: 300 in each group	335	300	90	35	7	Adverse events: 5 (2%)	25 (7%)	335	275	82	60	18	Adverse events: 3 (1%)	45 (13%)	8
HEAD TO HEAD WEIGHT TRIALS																
STEP-8, 2022	(3:1): 126 in each group and 84 in the control group	253: sema:126 and lira:127	201	sema: 109 (86.5%) and lira: 92 (72.4%)	38	sema: 12 (9.5%) and lira: 26 (20.5%)	Sema: adverse events: 3 (2%) and other reasons: 9 (7%); lira: adverse events: 14 (11%) and other reasons: 12 (9%)	Losses: sema: 6 (5%) and lira: 9 (7%)	85	70	82.4	11	13	Adverse events: 3 (4%) and other reasons: 8 (9%)	Losses: 4 (5%)	-
CLINICAL OUTCOME TRIALS																
SELECT, 2023	8750 in each group	8803	6193	70.3	2351	26.70 %	Adverse effects: 1417 (16.1%), other causes: 934 (10.6%)	Loss to follow-up 192 (2%), withdrawal of consent 67 (1%)	8801	6439	73.2	2078	24	Adverse events: 689 (8%) and others: 1489 (16%)	Lost to follow-up 284 (3%), withdrawal of consent 96 (1%)	-2.9

The data in this table are an approximation since they have been calculated with the data published by the authors and comparing and modifying with the data obtained in https://www.clinicaltrials.gov/
In many cases the published data do not allow us to distinguish between discontinuation of treatment and true abandonment of the trial, nor the causes of the latter.

Table 3. Description of the populations included in each study, the variables studied and possible biases.

ARTICLE	REACHES SUFFICIENT SAMPLE SIZE TO MAKE INFERENCE	STUDIED POPULATION	OVERWEIGHT INTERVENTION (%)	CONTROL OVERWEIGHT (%)	MAIN VARIABLE	ADDITIONAL INTERVENTION TO TREATMENT	POTENTIAL CONFLICT OF INTEREST	POSSIBLE LIMITATIONS OF THE STUDY			THEY SUSPEND TREATMENT DURING FOLLOW-UP	POTENTIAL CONFOUNDERS
SCALE, 2015	No	80% White women, middle age: 41 to 48 years, obesity II	2.7	3.5	Surrogate: weight change	Lifestyle intervention: nutritional counseling and physical activity	Sponsored pharmaceutical industry	Missing values were imputed using the last observation carried forward method for measurements taken after baseline.	Results are presented only if an effect was demonstrated.		Intervention 28% and control 35.6%	Includes overweight women without stratifying.
STEP-1, 2021	No	74% Non-Hispanic or Latino white women, average 45 years old, obesity II	6.2	5.5	Surrogate: weight loss of >5%/% weight change	Lifestyle intervention: nutritional counseling and physical activity	Directed and sponsored pharmaceutical industry	Comparison of groups: lack of hormones, treatments, countries; results: how many patients finish with 1/2 dose.	The sample size has not been calculated for the study of changes in body composition using absorptmetry, it is a secondary variable.		Intervention 18.9% and control 27.2%	Includes overweight women without stratifying.
STEP-3, 2021	No	81% Non-Hispanic or Latino white women, average 45 years old, obesity II	5.7	7.4	Surrogate: weight loss of >5%/% weight change	Lifestyle intervention: nutritional counseling (intensive diet) and physical activity. In addition to behavioral therapy	Directed and sponsored pharmaceutical industry	Comparison of groups: missing hormones, endocrine pathology, treatments, additional diet and behavioral intervention. "similar to an intention-to-treat analysis".			Intervention 17.9% and control 18.6%	Includes overweight women without stratifying.
STEP-5, 2022	No	78% White women, average 47 years old, obesity II	Does not appear	Does not appear	Surrogate: weight loss of >5%/% weight change	Lifestyle intervention: nutritional counseling and physical activity	Sponsored pharmaceutical industry	Missing values were imputed using the average treatment effect for the treatment period across all participants.		They change the scales on the adverse effects graphs so that they seem almost imperceptible when they are reaching 82% of people treated with semaglutide.	Intervention 23.68% and control 38.82%	Includes overweight women without stratifying.
SURMOUNT-3, 2023	No, they need 300 in each group for a statistical power of 90%	63% White women, average 46 years old, obesity II*	5.7	7.4	Surrogate: weight loss of >5%/% weight change	Intensive lifestyle intervention: nutritional counseling and physical activity	The sponsor (Eli Lilly) contributed to the study design, supervised the conduct of the study, and provided medical writing and editorial support for this article.	Randomization is after intensive lifestyle treatment, after which 227 patients who could be the least motivated are lost.	Missing data will be imputed using all non-missing data from the primary outcome measurement from the same treatment arm	The dose achieved may be 10 or 15 mg, but it is not specified or stratified by this variable.	Intervention 21.3% and control 30.5%	Includes overweight women without stratifying.
WEIGHT RECOVERY TRIALS												
STEP-4, 2021	No	79% Mujeres blancas, media 46 años, obesidad II	2.7		Surrogate: weight change	Lifestyle intervention: nutritional counseling and physical activity	Sponsored pharmaceutical industry	Missing values were imputed using the average treatment effect for the treatment period across all participants.			Intervention 7.29% and control 11.94%	Includes overweight women without stratifying.
SURMOUNT-4, 2024	No, they need 300 in each group for a statistical power of 90%	71% White women, average 48 years old, obesity II*	2.7		Surrogate: weight % change	Intensive lifestyle intervention: nutritional counseling and physical activity	The sponsor (Eli Lilly) designed and supervised the conduct of the trial; Trial site investigators were responsible for data collection and the sponsor conducted site monitoring, data collection, and analysis.	Until week 36, everyone received a dose of treatment, so the side effects of the placebo group can be difficult to differentiate if they are not really a side effect of the previous treatment.	The mean treatment effect of tirzepatide relative to placebo is calculated for all participants who had undergone randomization, regardless of treatment adherence.	The dose achieved may be 10 or 15 mg, but it is not specified or stratified by this variable.	Intervention 10.45% and control 17.91%	Includes overweight women without stratifying.
HEAD TO HEAD WEIGHT TRIALS												
STEP-8, 2022	No	79% White women, average 46 years old, obesity II	71	8.7 lira; 4.7 placebo	Surrogate: weight % change	Lifestyle intervention: nutritional counseling and physical activity	Directed and sponsored pharmaceutical industry	Sema reduces dose if necessary and with lira withdraws if side effects.	A multiple imputation approach 16 was used in which missing data were imputed by sampling measurements available at week 68 from participants in the same treatment group and with the same treatment completion status.	Percentages not absolute values and the same importance to the main variable as to secondary variables.	Intervention: 13.5% and 27.6% and control: 17.6%	Includes overweight women without stratifying.
CLINICAL OUTCOME TRIALS												
SELECT, 2023	No	72% White men, average 62 years, obesity I AMI	29	28.1	Added: cardiovascular death, heart attack and stroke	Standard care	Directed and sponsored pharmaceutical industry	Ends the study at 34 weeks (overestimates results and minimizes adverse effects).	Permanent termination of the trial early due to adverse events.	Added variable neurological adverse effects: central and peripheral, unspecified.	Intervention 30.8% and control 24.3%	Includes unstratified overweight men.

Table 4. Absolute efficacy of GLP1a.

TEST ↓ PLG1 WEIGHT VS PLACEBO

REHEARSAL	1st AUTHOR	EFFECTIVENESS								
		Average weight (Kg)	Average BMI	Weight loss (%)	Weight loss (Kg)	Loss ≥5% weight (%ptes)*	Loss ≥10% weight (%ptes)*	NNT for loss ≥5%	NNT for loss ≥10%	BMI change
SCALE	Pi-Sunyer 2015	106.2 ± 21.2	38.3 ± 6.4	-5.4 (-5.8 to -5.0)	-5.6 (-6.0 to -5.1)	36.1	22.5	3	4	-1.9
STEP-1	Wilding 2021	105.4 ± 22.1	37.8 ± 6.7	−12.44 (−13.37 to −11.51)	−12.7 (−13.7 to −11.7)	54.9	57.1	2	2	−4.61
STEP-3	Wadden 2021	106.9 ± 22.8	37.8 ± 6.7	-10.3 (-12 to -8.6)	-10.6 (-12.5 to -8.8)	39.0	48.3	3	2	-3.8
STEP-5	Garvey 2022	105.6 ± 20.8	38.6 ± 6.7	−12.6 (−15.3 to −9.8)	−12.9 (−16.1 to −9.8)	42.7	48.5	2	2	-4.3
SURMOUNT-3	Wadden 2023	110.1 ± 23.9	38.7 ± 6.6	−20.8 (−23.2, −18.5)	−25.0 (−26.9, −23.2)	71	67.8	1	1	-8.9

WEIGHT TRIALS SEMA VS LIRA VS PLACEBO

REHEARSAL	1st AUTHOR	EFFECTIVENESS							
		Average weight (Kg)	Average BMI	Weight loss (%) week	Weight loss (%) LIRA	Weight loss (%) placebo	Loss ≥10% SEMA weight (%ptes)	Loss ≥10% LIRA weight (%ptes)	NNT loss ≥10% weight SEMA vs LIRA
STEP-8	Rubino 2022	102.5	37	−15.8 (−17.6 to −13.9)	−6.4 (−8.2 to −4.6)	−9.4 (−12.0 to −6.8)	70.9	25.6	2

WEIGHT RECOVERY TRIALS

REHEARSAL	1st AUTHOR	PESO MEDIO (KG)	IMC MEDIO	DURACIÓN TRATAMIENTO INICIAL	PÉRDIDA PESO INICIAL (%)	TRATAMIENTO TRAS ALEATORIZACIÓN	CAMBIO PESO (%) GRUPO CONT	CAMBIO PESO (%) GRUPO SUSP	% PESO RECUPERADO (RESP PÉRDIDA INICIAL)
STEP-4	Rubino 2021	107.2 ± 22.7	38.4 ± 6.9	20 weeks	-10.6 ± 4.7	48 weeks	-7.9 (-8.6 to -7.2)	6.9 (5.8 to 7.9)	65
SURMOUNT-4	Aronne 2023	107.3 ± 22.3	38.4 ± 6.6	36 weeks	-20.9 ± 7.3	52 weeks	-5.5 (-6.8 to -4.2)	14 (12.8 to 15.2)	67

CLINICAL OUTCOME TRIALS

REHEARSAL	1st AUTHOR	AVERAGE WEIGHT (Kg)	AVERAGE BMI	WEIGHT LOSS (%)	WEIGHT LOSS (KG)	BMI CHANGE	CV COMBINED VARIABLE DIFFERENCE (%)	COMBINED VARIABLE NNT	DIFF DEATH CV (%)	DIFF % INFARCTION	DIFF % STROKE	DIFF. % DEATH FROM ANY CAUSE
SELECT	Lincoff 2023	96.5 ± 17.5	33.3 ± 5.0	-8.51 (-8.75 to -8.27)	8.21*	-2.8	-1.5	67 (43-143)	-0.5 (not next)	-1 (not next)	-0.2 (not next)	-0.9 (not next)

(*) Difference between the proportion of patients who achieve said weight loss in the intervention group and in the placebo group.

Table 5. Analysis of the % of adverse events and calculation of the NNH in each study.

REHEARSAL	1st AUTHOR	DIARRHEA				VOMITING				ABDOMINAL PAIN				PANCREATITIS				GALLBLADDER PATHOLOGY				BREAST CANCER				THYROID CANCER				PSYCHIATRIC PATHOLOGY				SERIOUS			
		% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI	% GI	% GC	NNH	95% CI
TEST ↓ WEIGHT F VS PLACEBO																																					
SCALE	Pi-Sunyer 2015	24	12	9	7-11	19	5	7	6-9	14	9	21	15-38	0.3	0.1	414	-	2	1	61	42-123	0.4	0.2	414	-	0.1	0.0	829	-	0.1	0.2	2491	-	6	5	83.0	37-246
STEP-1	Wilding 2021	31	16	6	5-9	25	7	6	5-7	19	11	12	9-19	0.2	0.0	653	-	2	0.2	73	45-205	0.2	0.2	1298	-	0.1	0.0	1306	-	0.2	0.0	435	-	10	6	29.0	17-129
STEP-3	Wadden 2021	36	22	7	5-16	27	11	6	4-10	21	7	7	5-12	NC	NC	NC	-	3	0.0	31	19-108	0.2	0.5	-409	-	0.2	0.0	407	-	0.2	0.0	407	-	9	3	16.0	10-49
STEP-5	Garvey 2022	35	24	9	5-105	30	5	4	3-6	28	9	5	4-10	NC	NC	NC	-	3	0.0	38	-	0.0	1	-76	-	NC	NC	NC	-	6	8	-51	-	8	12	-26.0	9-34
SURMOUNT-3	Wadden 2023	31	9	5	4-7	18	1	6	5-8	10	2	12	8-24	0.3	0.3		-	2	1	94	-	2	1	140	-	2	1	140	-	21	19	41	-	6	5	91.0	-
WEIGHT RECOVERY TRIALS																																					
STEP-4	Rubino 2021	14	7	14	9-37	10	3	14	10-29	10	4	17	11-47	NC	NC	NC	-	1	1	267	-	1	0.0	178	-	NC	NC	NC	-	NC	NC	NC	-	8	6	48.0	18-53
SURMOUNT-4	Aronne 2023	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	NC	NC	NC	-	3	3	-	-
HEAD TO HEAD WEIGHT TRIALS																																					
STEP-8	Rubino 2022 (sema vs lira)	28	18	10	NS	25	21	20	NS	6	4	42	NS	NC	NC	NC	NC	1	3	-42	NS	1	2	-128	NS	NC	NC	NC		6	15	-11	-6 - -49	8	11	-32.0	NS
CLINICAL OUTCOME TRIALS																																					
SELECT	Lincoff 2023	14	6	12	11-14	14	6	12	11-14	14	6	12	11-14	0.2	0.3		-	3	2	205	105-4609	5	5	2254	-	5	5	2254	-	6	7	59	42-98	33	36	-33.0	-23-(-63)

GI Intervention group. **GC** Control group. **NC** Not stated.
Note: The data in this table come from ClinicalTrials.gov (except SELECT which does not have results published on that page). SAEs come from published studies.
SURMOUNT-3 and SELECT do not differentiate the types of neoplasm (gives grouped data) and SELECT does not differentiate gastrointestinal pathology.
Note: NNH has been calculated with the data in table 2 (people who initiated tto) and the data in this table.

GLP1a for weight loss

Design

All trials included followed a similar methodology. They are randomised, phase-3 trials with different degrees of masking. The main outcomes are absolute weight loss (kg) or loss relative to initial weight (%) and the proportion of patients who achieve a pre-established weight loss (5%, 10%, 15%). Changes in cardiometabolic variables (glycated haemoglobin, systolic or diastolic blood pressure, total change. HDL or LDL, abdominal girth, etc.) were measured as secondary outcomes, and quality of life was assessed using various questionnaires.

Although randomisation was 1:1 in most trials, in some cases it was unbalanced (2:1, 3:1). It should be noted that several of the trials studied did not achieve the sample size calculated in the protocol to be able to reach a conclusion. Follow-up in these trials varied between 56 and 104 weeks.

According to their respective protocols, the trials aimed to include a population with overweight or obesity, older than 18 years, and of any age or sex. However, the included sample was mainly Caucasian women with a mean age of less than 50 years and a mean BMI corresponding to grade II obesity. The proportion of patients with overweight was limited in all trials (2.7–8.7%). In addition, some trials (STEP) excluded patients with mental health problems, which are commonly associated with obesity[27].

The majority of trials compared GLP1a with placebo, and only one compared the efficacy of two different GLP1a (semaglutide versus liraglutide). No trial compared GLP1a with other drugs approved for obesity treatment.

Interventions aimed at improving the diet and increasing physical exercise were carried out in the both the intervention and control groups. These programs, which tended to be intensive, were based on behavioural-modification techniques and supported by other elements such as applications.

Finally, although very few patients abandoned the trial, a significant proportion of patients discontinued the intervention, for different reasons, in both the intervention (between 10% and 21%, depending on the trial) and control groups (between 7% and 38%). withdrawals were more common in the intervention group in all trials (difference of between 1% and 15%).

Efficacy

Patients who received a GLP1a lost more weight than patients treated with placebo in all trials. The weight loss with respect to placebo was between 5.4% (liraglutide) and 20.8% (tirzepatide). This difference was statistically and clinically significant, as per the significance threshold required by the EMA28 (loss of at least 5% of initial weight). The Number Needed to Treat (NNT) to achieve a weight loss of at least 5% was between 1 (tirzepatide) and 3 (liraglutide) in the various trials, and between 1 (tirzepatide) and 4 (liraglutide) for a weight loss of 10%.

In the only trial to compare different GLP1a, the weight loss achieved with semaglutide was significantly higher than that achieved with liraglutide. This superiority reached the threshold of clinical significance (weight loss of 15.8% with semaglutide vs. 6.4% with liraglutide).

In the studies designed to determine the effect of suspending treatment (STEP-4[23] and SURMOUNT-4[24]), it was found that some of the lost weight was regained in the months following suspension of the drug. In these trials, follow-up was halted at 48 and 52 weeks, respectively. At that stage, patients had regained around two thirds of the lost weight.

None of the studies included in this section evaluated the effect of these drugs on morbidity and mortality.

Adverse events

Although the trials have very similar designs, there are differences in terms of the way in which adverse events are reported. These events were more prevalent, and tended to cause more withdrawals, in the intervention group. The most common such events in this group were gastrointestinal (diarrhea: affected 24–36% of patients, depending on the study; vomiting: 18–30%; abdominal pain: 10–28%) and were more prevalent at the onset of treatment. The number needed to harm (NNH), as calculated for each study, was between 5 and 21 for the different gastrointestinal events in the different trials.

The adverse events grouped under the term hepatobiliary system (such as cholecystitis, gall stones, etc.) were less common, with an NNH of 31 (19–108) in the STEP-3 trial[20].

Serious adverse events also tended to be gastrointestinal and hepatobiliary, with a frequency corresponding to an NNH of between 16 and 91 for the various trials. Other adverse events, such as pancreatitis or neoplasms, were rare and did not appear to be more common in the intervention group.

Limitations

One important limitation of these trials is that efficacy was demonstrated using a surrogate outcome (weight loss); they were not designed to confirm that said loss had health-related outcomes (reduced morbidity and mortality).

Moreover, although these studies recruited a population older than 18 years of any sex, the population that finally participated was mainly female (between 63% and 80%), depending on the study, was a mean age of between 41 and 48 years. Similarly, although the trials intended to demonstrate the efficacy of GLP1a in overweight and obesity, the proportion of patients with overweight was limited: the mean BMI corresponded to grade II obesity.

In addition, the sample size required to reach a conclusion was not achieved, considering patients who completed the full treatment, which results in a corresponding loss of accuracy and validity[29]. The proportion of patients who discontinued the intervention is particularly noteworthy as this limits the information available and may overestimate the efficacy and underestimate the adverse events related to GLP1a.

Finally, all trials were sponsored by the pharmaceutical company holding the patent for the drug. In most cases, this company designed the trial, supervised its conduct, analysed the data and supported drafting of the subsequent publication. A large proportion of the authors of the articles for these trials have a significant conflict of interest with the company sponsoring the trial.

GLP1a for the secondary prevention of cardiovascular disease

Design

The SELECT[26] trial is a randomised, triple-blind, phase-3 trial that compared subcutaneous semaglutide versus placebo. The primary outcome was a composite outcome comprising death by any cardiovascular cause, stroke or heart attack.

Randomisation was 1:1. The sample size was calculated based on the incidence of major cardiovascular events. A total of 1225 such events were required for a statistical power of 90%, and this was achieved by summing the 569 for the 8803 patients (6.5%) in the semaglutide group and the 701 for the 8801 patients (8.0%) in the placebo group. Mean follow-up was 3.3 years.

A population with a BMI ≥ 27 kg/m^2, older than 45 years and of either sex, with a prior diagnosis of cardiovascular disease (myocardial infarction, stroke, symptomatic peripheral arterial disease), was included. During follow-up, 27% and 24% of patients in the intervention and placebo groups, respectively, discontinued the intervention.

The largest sub-population included in the study was white males, with a mean age of 62 years and a history of myocardial infarction. The mean BMI for the patients included corresponded to grade I obesity. In comparison with the trials discussed above, the proportion of patients with overweight (29%) should be noted. In this case, patients with class IV heart failure and with severe psychiatric disorders were excluded.

The trial compared subcutaneous semaglutide with placebo and with no lifestyle intervention other than the advice recommended in standard clinical practice (non-intensive intervention).

Efficacy

Treatment with semaglutide for 39.8±9.4 months reduced the risk of suffering a cardiovascular event by 20% (HR = 0.80; 0.72–0.90). The absolute reduction in the primary outcome was 1.5%, which corresponds to an NNT to reduce an event of 67 (44–143) for 3.3 years. The difference in the first secondary outcome (cardiovascular mortality) was not statistically significant, therefore, according to a hierarchical analysis, the statistical significance of the remaining outcomes was not calculated, and it was also not calculated for each individual component of the outcomes. In any case, the observed numerical results are consistent with those for the composite outcome.

Adverse events

As was the case for the weight-loss trials, gastrointestinal problems, which were mainly responsible for patients discontinuing treatment, were most notable. The proportion of patients discontinuing treatment was slightly higher in the intervention group than in the control group (26.70% vs. 23.70%, respectively). Adverse events, the incidence of which in the intervention group was twice that for the control group (16.6% vs. 8.2%, respectively), were mainly responsible for these discontinuation.

In the SELECT trial[26], serious adverse events were more common in the placebo group (absolute increase in incidence of 3%). This may be due to the fact that cardiovascular outcomes which were included in the efficacy results were also included as adverse events. In this regard, the higher frequency of hepatobiliary adverse events in patients treated with semaglutide (2.8% vs. 2.3%) should be noted. In contrast, a lower incidence of events such as infections, central and peripheral nervous system disorders and medical and surgical procedures was found for the semaglutide group.

Limitations

First of all the population included mainly comprised white males with grade I obesity who had suffered acute myocardial infarction. Discontinuation of the intervention during follow-up exceeded 20%.

Although, in contrast to the aforementioned trials, the outcome variables are clinically relevant (rather than surrogate), a combined outcome was employed, which may result in an overestimation of efficacy. In addition, although the primary outcome was significant, the significance of the individual and secondary outcomes was not determined, thereby limiting the information available from the trial.

The trial was designed and sponsored by the pharmaceutical manufacturer, which also reviewed the manuscript. Moreover, several of the authors are employees of that company and others have different commercial relationships with pharmaceutical companies.

Discussion

GLP1a have demonstrated efficacy for weight loss in patients with obesity in several clinical trials. This weight loss reached the threshold defined as clinically significant (loss ≥5% of initial weight), exceeding the threshold of 10% in a large proportion of patients, and was maintained while treatment continued.

Two recent meta-analyses support the efficacy of GLP1a for weight loss in patients with obesity. With respect to placebo, GLP1a produce a mean weight loss of 5.3 kg (4.2–6.5),[30] or 5.8% (5.3–6.3%).[31] In comparison with other drugs, indirect comparisons seem to show that GLP1a are one of the most effective families (together with phentermine/topiramate, which is not marketed in Spain).[31] None of these studies included tirzepatide.

Moreover, in the only trial published to date to evaluate morbidity and mortality, in a context of secondary prevention, treatment with semaglutide for three years resulted in an absolute reduction of the risk for the composite cardiovascular outcome (death by any cardiovascular cause, stroke or heart attack) of 1.5%. The most important effect of semaglutide appears to be the reduction of non-fatal heart attacks although, individually, the components of the composite outcome are not statistically significant. The reduction in all-cause mortality is also not statistically significant.

Although the construction of this composite outcome is acceptable, it is still subject to the uncertainty inherent to such variables. Firstly, the severity of the individual outcomes included is not equivalent: the functional prognosis of a stroke is very different to that of a heart attack, and both are qualitatively different to death as the outcome.

In any case, despite these clarifications, SELECT[26] is important as it is the only trial which have demonstrated the efficacy of GLP1a in clinically relevant (and non-surrogate) outcomes in the non-diabetic population. Despite this, it remains to unclear whether these findings are due to an independent effect of semaglutide or they can be fully attributed to the weight loss. Although the SELECT would have been a good opportunity to study this, in contrast to the other trials, an intensive lifestyle intervention was not applied in the control group[32].

If we take a closer look at the topic of surrogate outcomes, and revisit the weight-loss trials, the clinical significance of the loss achieved with these drugs can be questioned. Although the findings are robust, and were obtained from well-designed studies, the weight loss remains a surrogate (replacement or intermediate) outcome for the actual aim, namely to improve health and delay disease and death.

The reduction in the severity of obesity achieved with GLP1a is, in general, modest. In the majority of clinical trials the mean BMI of the participants corresponds to grade II obesity. Despite the weight loss achieved, liraglutide does not modify the severity of obesity (in other words, patients remain, on average, with grade II obesity); patients with semaglutide changed to grade I obesity. Tirzepatide is the only drug that has shown to revert a mean BMI of grade II obesity to a mean BMI corresponding to overweight.

In addition, in these trials, reference is made to the "clinically significant" threshold for weight loss, which is 5% of the initial weight, a criterion established by the EMA for the approval of such drugs[28]. However, the evidence supporting the 5% threshold is only based on surrogate outcomes (cholesterol, blood pressure, HbA1c, etc.)[33,34], therefore the actual clinical significance thereof remains uncertain. Indeed, the findings of the SELECT trial[26] support this. In this trial, high-risk participants (obese, with established cardiovascular disease) lost a mean of 8.5% of their initial weight but, despite that, the absolute reduction in the risk of cardiovascular events was only modest.

Consequently, it is logical to suppose that a lower weight loss in patients with better baseline health will result in even smaller benefits: in other words many more patients will need to be treated for longer to achieve a minimum benefit. In summary, there are reasons to question the clinical threshold used in these trials and, consequently, to reinterpret the conclusions of the GLP1a trials. In any case, the reversion of the weight loss observed upon suspension of treatment should also be added to these limitations.

With regard to the methodology used in the trials discussed in this Bulletin, although the design and execution thereof are acceptable, some limitations may reduce their internal validity. In the majority of cases, if we consider the patients who actually continued with the intervention, the sample size required to be able to perform a statistical inference was not reached. Moreover, randomisation is 2:1 in several trials and 3:1 in another, a strategy which may, on occasions, reduce the internal validity of clinical studies[35].

The external validity of trials may also be compromised by various aspects. In the majority of weight-loss studies, middle-aged women with grade II obesity are over-represented. The proportion of patients with overweight was minimal in all trials, therefore the findings thereof may not be extrapolable to this population.

In addition, there are other limitations to applicability, such as the lack of stratification of the results (by age, sex, BMI, etc.), which prevents us from knowing the efficacy in relevant groups of patients. These groups include patients older than 65 years, in which the harmful effects of excess weight appear with higher BMI values than in younger patients[6].

Finally, a substantial proportion of people with obesity do not receive the lifestyle intervention that both groups received, especially its intensive version[36]. The effectiveness of the drug as an isolated intervention in the heterogeneous population seen in our clinics will probably be lower than that reported in the trials.

One marked limitation of these trials is the high proportion of patients who discontinued treatment. Moreover, discontinuation is more common in the intervention group than in the control group. This reduces the confidence in the efficacy and safety data, possibly overestimating the former (survival bias, missing data imputation method) and underestimating the latter. Other factors, such as division into multiple sub-groups, limited treatment time and follow-up time after suspension, may also have resulted in an underestimation of the adverse events.

Indeed, discontinuation of treatment is often related to adverse events. The high frequency of gastrointestinal adverse events found in all studies (especially diarrhoea, vomiting and abdominal pain) should be noted. The proportion of patients who suffered serious adverse events (mainly gastrointestinal and hepatobiliary) is high, with an NNH of between 16 and 91 in the various trials.

Other adverse events, such as pancreatitis or neoplasms, were rare in these trials, thus preventing firm conclusions from being reached. However, and although the absolute risk is low, observational studies have reported that GLP1a multiply the risk of suffering pancreatitis by nine[37].

Moreover, preclinical studies showed that medullary thyroid tumours are a class effect of GLP1a[38]. In contrast, in clinical terms, in a large cohort with a mean follow-up of 4 years, treatment with GLP1a for diabetes was not related to a higher incidence of thyroid cancer[39]. In any case, given the association found in previous case-control studies[40], the fact that the doses used in obesity preparations are higher than those used for diabetic patients, and given the latency time required to develop this type of tumour, the cancer incidence should be monitored.

GLP1a have also been associated with other adverse events, such as gastroparesia, intestinal obstruction and complications during anaesthesia, given their effect on gastrointestinal motility[37]. With respect to psychiatric adverse events, despite the alerts[41] issued in the summer of 2023, the EMA has recently ruled out the relationship between these agents and a tendency to self-harm[42].

Regaining the lost weight in those patients who suspend treatment may entail a worse prognosis with respect to patients who never received the drug. According to data collected using dual-energy X-ray absorptiometry (DEXA) for subgroups in these trials, the weight loss induced by GLP1a is due to the loss of both lean and fatty mass, although the latter is lost to a greater extent. Despite this, the loss of lean mass is equivalent to at least a decade of ageing, and the decrease in muscle mass (sarcopenia, frailty) is strongly related to morbidity and mortality[43].

After finishing treatment, regaining the lost weight is unlikely to be due to an increase in muscle mass[43]. Consequently, after treatment with an GLP1a, a patient, with the same weight, may have a higher proportion of adipose mass, with the resulting adverse consequences, which would be in addition to the harmful effects of the loss of muscle mass itself. In such cases, GLP1a may have a net harmful effect, and this aspect should be studied given the high proportion of discontinuation in both clinical trials and real life[44]. In any case, it has been suggested that exercise may modulate these changes, reducing the lean loss during GLP1a treatment and the recovery of fat after suspension thereof[43,45].

Although the experience with the use of GLP1a in patients with type 2 diabetes appears to indicate that these drugs are safe, these findings should not be extrapolated automatically to new indications. The doses used for weight loss are higher and the patient profile is different, therefore adverse events should be monitored with care. In particular, special attention should be paid to rare adverse events (which, therefore, are not detected in clinical trials), those with a high latency and the outcomes of patients who regain the lost weight after using a GLP1a.

Finally, the lack of independence in biomedical research considerably reduces confidence in the results[46]. In this sense, it should be pointed out that all the trials analysed were sponsored by the pharmaceutical company holding the patent for the drugs studied. Moreover, in a therapeutic area with a potential market of thousands of millions of people, the incentives to extend prescription as much as possible are very powerful.

In summary, the GLP1a analysed, within the indications studied and as the various uncertainties analysed in this bulletin are resolved, could occupy a place in the toolbox for the management of certain cases of obesity, or for improving the prognosis in secondary prevention of cardiovascular disease, as will be developed below.

However, various social factors may encourage an inadequate use of GLP1a for non-health related reasons, as obesity is a risk factor with very different implications to others such as hypertension or hypercholesterolaemia. In addition, the conceptualisation of obesity with which these drugs are being promoted could, paradoxically, be an obstacle in the aetiological approach to the epidemic. The relevance of all these factors deserves a detailed analysis.

Obesity in context: much more than health

In contrast to other risk factors, excess weight is an observable characteristic[47], thus meaning that its consideration transcends the medical field and is closely related to aesthetics and other social ideals and conventions. For example, values related to the economic system (protestant work ethic, meritocracy myth, etc.) encourage the perception that overweight or obese people are like that due to laziness or a lack of self-discipline[47,48]. Similarly, the aesthetic pressure to achieve an unreachable (and excessively thin) ideal body, which disproportionately affects women[49], judges obesity from a view point of aversion and rejection. Here we find a number of factors that may promote GLP1a treatment for non-health reasons.

This stigmatisation of obese people, also known as weight bias or "fatphobia" (negative attitudes, belief, assumptions and opinions related to weight[47]), reaches fields as diverse as health care, employment, education or interpersonal relations[50]. Indeed, far from helping, fatphobia increases the risk of mental disorders (stress,

depression, anxiety and even a tendency to self-harm), promotes problematic behaviours that may worsen the excess weight (binge eating, avoiding physical exercise) and may have direct consequences on physical health[47,48,51]. Stigmatisation in the health system, in turn, affects the quality of care, its continuity, and adherence to treatment[51].

This stigmatising perspective is closely related to the debate about the causes of obesity, which has rekindled with the arrival of GLP1a. This discussion, in turn, is closely related to the strategies proposed to combat this epidemic[5]. If a positive energy balance is responsible for the obesity, as explained in the introduction, it is essential to identify the causes of this cause, the drivers: What factors explain the increase in behaviours that lead to a positive energy balance over the past few decades?

Biology cannot be the answer, as it has not undergone a substantial change so quickly[52]. The bulk of the debate therefore lies between two opposing positions regarding the attribution of human behaviour: an individualistic approach that places the predominant responsibility in the individual, and a structural or systemic approach that places greater emphasis on environmental and social factors[5].

The individualistic approach relies on concepts such as free will or the responsibility for one's own behaviour[5]. The behaviours that lead to obesity would therefore be decisions taken freely and, therefore, the responsibility (and fault) of the obese person. This perspective is closely related to the stigma associated with obesity discussed above[50]. However, internalising the causes of the behaviour only displaces the question, which still needs to be explained[53] why are these choices made more frequently now than before?

In contrast, the structural perspective suggests that different environmental factors, through their influence on biological, psychological and socio-economic vulnerabilities, promote the behaviours that cause and maintain obesity[5]. This perspective allows us to study the contextual changes that have occurred in recent decades and that could therefore explain the obesity epidemic.

Although factors related to mobility and city planning[52,54], which encourage a sedentary lifestyle, have an effect, the most important *drivers* are found in the food system[54]. These include a greater availability of ultraprocessed, calorie-rich, tasty and cheap food, improvements to the distribution systems that make this type of food an accessible and comfortable option, and a more extensive and targeted food marketing[54].

In summary, over the past few decades the context has been changed to reduce the decision-making capacity, such that it is increasingly easier (thanks to advertising, availability in supermarkets, low price, limited need for preparation, etc.) and more rewarding (products with high sugar, salt and additive contents, and low in satiating components such as proteins and fibre) to consume ultraprocessed food[52,54].

These habits, in turn, promote the rejection of government intervention in the food system and other factors (such as the regulation of private transport, for example)[54]. The success of ultraprocessed foods generates huge profits for the food industry, which is encouraged to perpetuate and improve the production and marketing of these products, along with the lobby against government intervention[54].

As is also the case for other health-related situations, the effects of this obesogenic environment are affected by various social determinants, such as the economy, education, characteristics of the area where the person lives, etc. Thus, irrespective of other clinical and demographic factors, obesity is both more common and more severe in people with socioeconomic difficulties[55]. The prevalence of obesity in Navarra is up to 53% higher in the lower income population (prevalence of 11.3% in people receiving the minimum guaranteed income vs 7.4% for higher incomes)[56].

Should we define obesity as a disease?

As we have seen, we could state that excess weight is the normal response of people to the obesogenic context in which they find themselves[5,52]. Despite this, GLP1a are being promoted by calls for obesity to be considered a medical disease[57]. Although it is argued that this definition would allow more and better resources to be devoted to this disorder and reduce the associated stigma[57,58], there are reasons to believe otherwise.

Thus, it is not necessary to classify obesity as a disease for it to receive resources, at least in countries with a welfare state[58]. The supposed beneficial effect on the stigma is based on mere speculations. Indeed, it may even increase, it as it would mean classifying the disorder as a pathological state deviating from the norm[58]. In addition, defining obesity as a medical disease may favour biogenetic explanations[59], which would mean diverting attention from the obesogenic context responsible for the epidemic.

Finally, this biomedical definition of obesity, together with some of the social factors mentioned above (stigma, aesthetics, gender, etc.), share a single outcome: promoting pharmacological over-treatment of the excess weight. Indeed, obesity is a risk factor, especially grades II and III. In contrast, as we have seen above, overweight appears to have no effect on mortality, and the risk resulting from grade I obesity is modest[6,58]. The vast majority of people with excess weight will never suffer from related diseases and will live as long as their counterparts with normal weight[58]. Defining obesity as a disease removes these nuances, and encourages the overestimation of the risks of excess weight that stigmatisation already produces[47].

The explanation for the proliferation of debates regarding the nature of obesity does not perhaps lie in the medical literature but, again, in the social determinants of health, in this case commercial ones. Over the past few decades the focus of numerous health problems has been redirected to maximise the profits of companies and their shareholders, as a result of their influence on science, and often resorting to the individualistic perspective explained above[60].

This strategy is repeated with GLP1a[61] .In Spain, for example, 61% of the population aged between 25 and 64 years is overweight or obese and, therefore, can be considered candidates for GLP1a treatment[3]. However, 39% of these are overweight and only 5.2% of the population has grade II obesity or worse[3]. The definition of excess weight as a disease determines the market share and opens the door to the treatment of billions of people worldwide.

This probably explains the generous sponsorship of the key opinion leaders (KOLs) who lead these debates and the medical conferences and training events where they take place, by GLP1a manufacturers.[61] Notwithstanding the uncertainties raised in this Bulletin, these events support the treatment of almost half the population with GLP1a for life as a solution to the obesity epidemic[61]. However, as explained, the apparently positive risk-benefit balance of GLP1a in the clinical trials published to date may disappear if they are administered to a healthier population.

During GLP1a treatment, the weight loss ceases at 12–18 months and, as we have seen, reverts if treatment is stopped.

The role of GLP1a in weight loss: still to be defined

Cost-effectiveness analyses contradict the above-mentioned expectations at the societal level, and even distance them from being a useful clinical tool in the individual patient. During GLP1a treatment, the weight loss ceases at 12–18 months and, as we have seen, reverts if treatment is stopped. Moreover, real-life use data indicate that only 27% of patients who started a GLP1a were still in treatment one year later[44]. These factors, amongst others, explain the findings of five-year cost-efficacy models, which suggest that bariatric surgery (sleeve gastroplasty) is superior to semaglutide. Finally, the cost of these drugs is excessive: to achieve the equivalence with surgery, the price of semaglutide should drop to around a third of the current price[62].

As such, the role of GLP1a in the care of patients with obesity remains uncertain. In light of the cost-effectiveness analysis presented, the role of GLP1a may be restricted to ensuring an initial weight loss for 12–18 months, with occasional reintroductions if required, in comprehensive programs with lifestyle and structural interventions[63]. Thus, the National Institute for Health and Care Excellence (NICE) in the UK recommends to use semaglutide in patients with a BMI ≥35 with at least one weight-related comorbidity (or BMI ≥30 with severity criteria), for a maximum of two years, only as part of a multidisciplinary weight-loss and weight maintenance program[64].

These recommendations differ from those in a clinical practice guideline published recently in Spain. The GIRO guideline, published by the Spanish Society for the Study of Obesity (SEEDO), has been drafted in collaboration with other medical societies and a patients' association.

It comprises 32 recommendations adapted from a Canadian guideline from 2020 and 89 new recommendations, designed after a systematic review, using the GRADE methodology.

This guideline proposes a more intensive pharmacological treatment strategy than NICE. Thus, it proposes to start weight-loss drugs in patients with a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 if they suffer from adiposity-related complications. In addition, it recommends to maintain treatment in the long term. Also noteworthy is the scant mention of the limitations of GLP1a, despite the uncertainty that accompanies any pharmacological novelty.

Another important limitation of the GIRO guideline is related to its editorial independence. Thus, the guidelines does not include a conflict of interest statement from the authors. Moreover, a recent study of payments to healthcare professionals in Spain shows that various directors of SEEDO are KOLs mainly funded by Novo Nordisk (which also funds the society and development of the GIRO guideline) and Eli Lilly[65].

The NICE perspective, which proposes a higher BMI threshold to that suggested in clinical trials to receive treatment, appears to be the most appropriate at this point in time. It is essential to adjust the prescription of GLP1a for weight loss to those patients in whom the risk-benefit balance is more favourable: severe obesity, obesity with comorbidities and secondary prevention of cardiovascular disease. Given the uncertainties that still surround GLP1a, given the health-related analysis of obesity, and in order to avoid overtreatment, we do not believe their use is warranted in overweight, and perhaps neither in class I obesity without comorbidities.

The need to adjust the indication for treatment is pressing for other reasons. The supply shortages for GLP1a presentations for type 2 diabetes is mainly due to the increased, off-label use thereof for weight loss in both the public and private sectors, perhaps more so in the latter[66]. Indeed, these drugs are being openly promoted and prescribed in the field of cosmetic medicine[67].

In addition, Wegovy® has arrived on the market before the supply problems for Ozempic® have been resolved, although the manufacturer, active substance, route of administration and even some dosages are the same. This nonsense, from a medical point of view, could perhaps be understood if we again adopt a commercial perspective.

Once again, clinical and class inequity appear to coincide in the various factors affecting the diversion of GLP1a towards weight loss, with the subsequent shortage for the treatment of diabetic patients: the aesthetic or quasi-aesthetic use deprives diabetic patients of proven health benefits. Fifty-three years after its definition, the inverse care law[68] remains operational: medical interventions, especially newer and more expensive ones, disproportionately reach the population with a better socioeconomic status and, therefore, generally with better health[66].

> NICE recommends to use semaglutide in patients with a BMI ≥35 with comorbidities (or BMI ≥30 with severity criteria), for a maximum of two years, only as part of a multidisciplinary weight-loss and weight maintenance program.

As we have seen, NICE limits the prescription of GLP1a to participation in a multidisciplinary weight-loss and weight maintenance program. However, as discussed above, access to such programs is limited. The majority of lifestyle interventions currently take place in clinics of Family and Community Care professionals. Unfortunately, the working conditions in health centres often prevent interventions from reaching the recommended degree of intensity. As such, the first step for improving the care of obese patients and improve access to such programs must involve the strengthening and adequate assignment of resources to Primary Care. Referral to specialised units must be reserved for the most severe or refractory cases, and should not be the only option due to a lack of time or resources at health centres.

Although it falls outside the scope of this Bulletin, the lifestyle interventions we undertake in our clinics should distance themselves from the traditional simple, authoritarian and uniform advice to "eat less and exercise more". As is the case for any intervention, lifestyle recommendations can have adverse outcomes. In this context, we could encourage inappropriate adherence to diets or

weight control methods, and lead to an exacerbation of body dissatisfaction caused by the aforementioned unattainable beauty ideal[69]. These are all specific risk factors for the onset of eating disorders, the incidence of which has been increasing for decades[70].

For lifestyle interventions, an approach based on respect for the person, that takes into consideration the specific aspects of each situation, as well as individual preferences, and which is based on the principles of behavioural modification, is probably much safer and effective. Through the interaction between professional and patient we would seek to create a context that brings the latter's behaviour closer to his or her health goals. In this approach, from the privileged perspective of Family and Community Care, and with support from other professionals (mainly psychologists and nutritionists), the aim should be to improve the diet and increase daily exercise.

Aetiological treatment is upstream; let's change focus

In any case, even if we manage to ensure access to intensive lifestyle interventions, and even though GLP1a are prescribed to the subgroups of patients who would receive the greatest benefit, it is essential to remember that the obesity epidemic will not go away if the structural factors responsible for it are not tackled. Indeed, as we have seen, it may even worsen if the biomedical perspective that permeates the promotion of GLP1a is adopted.

In a context designed to modify behaviour, interventions based on modifying individual decisions (education, appeal to responsibility, etc.) are highly unlikely to counteract the situation[5].

Moreover, the social determinants of obesity cannot be modified without political intervention, the most effective and cost-effective measures[5]. In addition to a health-based focus in all policies, governments must encourage the research, funding and implementation of systematic actions to modify the determinants of obesity[54]. Measures such as limiting the advertising of ultraprocessed foods aimed at young children, regulation of nutritional quality, the labelling of foods based on their composition or a tax on sugary drinks may help as initial approaches[5].

The enthusiasm for GLP1a, perhaps for now disproportionate, is probably better explained by aesthetics, stigma, commercial profitability and conflicts of interest than by unbiased and considered clinical analysis. It is important not to lose focus: the goal is not weight, but health. Interventions such as those mentioned, promoted by public health bodies, would benefit almost the entire population66, which is a victim of the harmful effects of ultraprocessed foods irrespective of their weight[71]. In this regard, the cost-effectiveness analysis discussed above should also include the cost-opportunity resulting from diverting an excessive proportion of care and resources to GLP1a, which will be received by a minority of patients and will benefit even fewer.

> It is essential to adjust the prescription of GLP1as for weight loss to those patients in whom the risk-benefit balance is more favourable: severe obesity, obesity with comorbidities and secondary prevention of cardiovascular disease.

By the time they arrive in our clinics, patients have long since fallen into the stream of harmful behaviours; many are already sinking in the river of disease[72]. As healthcare professionals, we must try and rescue them, that is, to maximise the safety and effectiveness of the interventions for the individual patient. These interventions are, in general, only modestly effective and will only allow us to rescue a few.

However, exclusive focus on downstream rescue is unlikely to improve the health of the population. Similarly, rescues based on lifestyle interventions will prevent only a few from slipping into disease. But the key action will be to point out the disease manufacturers which, upstream, are dragging large sectors of the population into the river. Upstream, a stroke of effective legislation will be more effective than the cumulative work of thousands of healthcare professionals over long periods of time[72].

With this Bulletin, from our perspective as family physicians, we advocate the importance of navigating all waters. However, we cannot forget that downstream, in our clinic, we will never have a drug that is comparable in terms of safety, efficacy and cost to the interventions undertaken upstream to modify the drivers of the environment that favours obesity.

To achieve the implementation of such policies we must create a context that encourages them, and the role of healthcare professionals may be key. Vigorous dissemination of this reality (to our patients, in our community, from the media, to governments, etc.) may well have a greater impact on the health of the population than the efforts aimed at prevention and treatment of each individual patient, one by one[72]. Let's pursue excellence in individual clinical care, but let's also venture upstream.

We do not believe their use is warranted in overweight, and perhaps neither in class I obesity without comorbidities.

Conclusions

The prevalence of obesity has increased over the past few decades to such an extent that it has become an epidemic. This excess adiposity is associated with an increase in morbidity and mortality, although the BMI alone is not sufficient to predict this.

Treatment with GLP1a, together with intensive lifestyle interventions, is effective for weight loss in obese patients, providing treatment is maintained, for at least two years.

The clinical significance of this weight loss is not well established and the weight is slowly regained after suspending treatment.

In patients with excess weight and established cardiovascular disease, treatment with semaglutide for three years reduces the risk of presenting a cardiovascular event by a modest amount. Given the limited number of overweight patients included in the trials, the benefit in this population remains uncertain.
The main limitations of the trials include the use of surrogate outcomes, the high proportion of treatment discontinuation, external validity problems and the lack of independence of the pharmaceutical industry.

The most common adverse events of GLP1a treatment are gastrointestinal and hepatobiliary. Gastrointestinal events affect a large proportion of treated patients. The incidence of serious adverse events is notable, and rare or highly latent adverse events should be monitored.

Various social (values, aesthetics, stigma) and economic factors (conflicts of interest, marketing, opinion leaders recruited by the industry) may encourage over-treatment of excess weight and the inappropriate use of GLP1a.

The role for these drugs in therapeutics remains to be determined. As such, it is essential to restrict their prescription to those sub-groups in which they are more likely to produce a benefit (severe obesity, obesity with comorbidities and secondary prevention of cardiovascular disease) and to specify their usefulness through studies and professionals free of conflicts of interest.

Accessibility to intensive lifestyle interventions needs to be ensured, mainly by strengthening primary health care.

The obesity epidemic has arisen due to changes in the context that encourage the behaviours associated with excess weight. Lifestyle interventions and drugs may help a minority of patients, but the solution to the epidemic requires upstream policy intervention on the social and commercial determinants of obesity.

References

1. OMS. Obesidad y sobrepeso. who.int. Published March 1, 2024. https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

2. Gobierno de Navarra. Plan de Salud Pública de Navarra 2022-2025. Published online January 1, 2023. https://www.navarra.es/NR/rdonlyres/75366057-0BD9-45A2-916F-61AC731CFA93/485645/PlandeSaludPublicadeNavarra20222025.pdf

3. Aranceta-Bartrina J, Pérez-Rodrigo C, Alberdi-Aresti G, Ramos-Carrera N, Lázaro-Masedo S. Prevalencia de obesidad general y obesidad abdominal en la población adulta española (25–64 años) 2014–2015: estudio ENPE. Rev Esp Cardiol. 2016;69(6):579-587. https://doi.org/10.1016/j.recesp.2016.02.010

4. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med Vol 5 No 7 April 14 2017 Ann Transl Med. Published online 2017. Accessed January 1, 2017. https://atm.amegroups.org/article/view/14394

5. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. The Lancet. 2015;385(9985):2400-2409. https://doi.org/10.1016/S0140-6736(14)61744-X

6. Visaria A, Setoguchi S. Body mass index and all-cause mortality in a 21st century U.S. population: A National Health Interview Survey analysis. PLOS ONE. 2023;18(7):e0287218. https://doi.org/10.1371/journal.pone.0287218

7. Suárez-Carmona W, Sánchez-Oliver AJ. Índice de masa corporal: ventajas y desventajas de su uso en la obesidad. Relación con la fuerza y la actividad física. Nutr Clínica En Med. 2018;12(3-2018):128-139. https://doi.org/10.7400/NCM.2018.12.3.5067

8. del Álamo A. Obesidad. Fisterra. Published online March 31, 2017. Accessed January 9, 2023. https://www.fisterra.com/guias-clinicas/obesidad/#

9. Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. Am Psychol. 2020;75(2):235-251. doi:10.1037/amp0000517. https://pubmed.ncbi.nlm.nih.gov/32052997/

10. Fármacos para la obesidad. INFAC. 2023;31(5):46-59. https://www.euskadi.eus/contenidos/informacion/cevime_infac_2023/es_def/adjuntos/Boleti-n-INFAC_Vol_31_5_Obesidad.pdf

11. Onakpoya IJ, Collins DRJ, Bobrovitz NJH, Aronson JK, Heneghan CJ. Benefits and Harms in Pivotal Trials of Oral Centrally Acting Antiobesity Medicines: A Systematic Review and Meta-Analysis. Obesity. 2018;26(3):513-521. https://doi.org/10.1002/oby.22118

12. Colquitt J, Pickett K, Loveman E, Frampton G. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014;(8). https://doi.org/10.1002/14651858.CD003641.pub4

13. Wiggins T, Guidozzi N, Welbourn R, Ahmed AR, Markar SR. Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: A systematic review and meta-analysis. PLOS Med. 2020;17(7):e1003206. https://doi.org/10.1371/journal.pmed.1003206

14. Prescrire International. Drugs to avoid 2024. Published online 2024. https://english.prescrire.org/en/1256/3059/60686/0/PositionDetails.aspx

15. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-662. https://doi.org/10.1016/S2213-8587(21)00203-5

16. AEMPS. La AEMPS actualiza la situación de suministro de los medicamentos análogos del GLP-1. AEMPS. Published April 24, 2024. https://www.aemps.gob.es/informa/la-aemps-actualiza-la-situacion-de-suministro-de-los-medicamentos-analogos-del-glp-1/#

17. Couzin-Frankel J. Obesity meets its match. Science. 2023;382(6676):1226-1227. https://doi.org/10.1126/science.adn4691

18. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015;373(1):11-22. https://doi.org/10.1056/NEJMoa1411892

19. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002. https://doi.org/10.1056/NEJMoa2032183

20. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP-3 Randomized Clinical Trial. JAMA. 2021;325(14):1403-1413. https://doi.org/10.1001/jama.2021.1831

21. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP-5 trial. Nat Med. 2022;28(10):2083-2091. https://doi.org/10.1038/s41591-022-02026-4

22. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023;29(11):2909-2918. https://doi.org/10.1038/s41591-023-02597-w

23. Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP-4 Randomized Clinical Trial. JAMA. 2021;325(14):1414-1425. https://doi.org/10.1001/jama.2021.3224

24. Aronne LJ, Sattar N, Horn DB, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA. 2024; 331(1):38-48. https://doi.org/10.1001/jama.2023.24945

25. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP-8 Randomized Clinical Trial. JAMA. 2022;327(2):138-150. https://doi.org/10.1001/jama.2021.23619

26. Lincoff A. Michael, Brown-Frandsen Kirstine, Colhoun Helen M., et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232. https://doi.org/10.1056/NEJMoa2307563

27. Leutner M, Dervic E, Bellach L, Klimek P, Thurner S, Kautzky A. Obesity as pleiotropic risk state for metabolic and mental health throughout life. Transl Psychiatry. 2023;13(1): 175. https://doi.org/10.1038/s41398-023-02447-w

28. CHMP. Guideline on clinical evaluation of medicinal products used in weight management. EMA. Published online June 23, 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-medicinal-products-used-weight-management-revision-1_en.pdf

29. García-García JA, Reding-Bernal A, López-Alvarenga JC. Cálculo del tamaño de la muestra en investigación en educación médica. Investig En Educ Médica. 2013;2(8):217-224. https://doi.org/10.1016/S2007-5057(13)72715-7

30. Liu Y, Ruan B, Jiang H, et al. The Weight-loss Effect of GLP-1RAs Glucagon-Like Peptide-1 Receptor Agonists in Non-diabetic Individuals with Overweight or Obesity: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. Am J Clin Nutr. 2023;118(3):614-626. https://doi.org/10.1016/j.ajcnut.2023.04.017

31. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet Lond Engl. 2024;403(10434):e21-e31. https://doi.org/10.1016/S0140-6736(24)00351-9

32. Fernández-Oropesa C. (NEJM) Eficacia cardiovascular de la semaglutida en personas obesas no diabéticas. Estudio SELECT. El Rincón de Sísifo. Published November 29, 2023. https://elrincondesisifo.org/2023/11/29/nejm-eficacia-cardiovascular-de-la-semaglutida-en-personas-obesas-no-diabeticas-estudio-select/

33. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? Obesity. 2015;23(12):2319-2320. https://doi.org/10.1002/oby.21358

34. Expert panel report: Guidelines (2013) for the management of overweight and obesity in adults. Obesity. 2014;22(S2): S41-S410. https://doi.org/10.1002/oby.20660

35. Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. Neurology. 2014;82(1):77-79. https://doi.org/10.1212/01.wnl.0000438226.10353.1c

36. Laddu D, Neeland IJ, Carnethon M, et al. Implementation of Obesity Science Into Clinical Practice: A Scientific Statement From the American Heart Association. Circulation. 0(0). https://doi.org/10.1161/CIR.0000000000001221

37. Ruder K. As Semaglutide's Popularity Soars, Rare but Serious Adverse Effects Are Emerging. JAMA. 2023;330(22):2140-2142. https://doi.org/10.1001/jama.2023.16620

38. Lisco G, De Tullio A, Disoteo O, et al. Glucagon-like peptide 1 receptor agonists and thyroid cancer: is it the time to be concerned? Endocr Connect. 2023;12(11):e230257. https://doi.org/10.1530/EC-23-0257

39. Björn Pasternak, Viktor Wintzell, Anders Hviid, et al. Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. BMJ. 2024;385:e078225. https://doi.org/10.1136/bmj-2023-078225

40. Bezin J, Gouverneur A, Pénichon M, et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care. 2023;46(2):384-390. https://doi.org/10.2337/dc22-1148

41. EMA. EMA statement on ongoing review of GLP-1 receptor agonists. Published July 11, 2023. https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists

42. PRAC. Meeting highlights from the Pharmacovigilance Risk Assessment Committee. EMA. Published April 12, 2024. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-april-2024

43. Locatelli JC, Costa JG, Haynes A, et al. Incretin-Based Weight Loss Pharmacotherapy: Can Resistance Exercise Optimize Changes in Body Composition? Diabetes Care. Published online April 30, 2024:dci230100. https://doi.org/10.2337/dci23-0100

44. Gleason PP, Urick BY, Marshall LZ, Friedlander N, Qiu Y, Leslie RS. Real-world persistence and adherence to glucagon-like peptide-1 receptor agonists among obese commercially insured adults without diabetes. J Manag Care Spec Pharm. 2024;30(8):860-867. https://doi.org/10.18553/jmcp.2024.23332

45. Jensen SBK, Blond MB, Sandsdal RM, et al. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomised placebo-controlled trial. eClinicalMedicine. 2024;69. https://doi.org/10.1016/j.eclinm.2024.102475

46. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017; 2(2):MR000033. https://doi.org/10.1002/14651858.MR000033.pub3

47. Alberga AS, Russell-Mayhew S, von Ranson KM, McLaren L. Weight bias: a call to action. J Eat Disord. 2016;4:34. https://doi.org/10.1186/s40337-016-0112-4

48. Puhl RM, Heuer CA. Obesity stigma: important considerations for public health. Am J Public Health. 2010;100(6):1019-1028. https://doi.org/10.2105/AJPH.2009.159491

49. Dutton GR, Lewis TT, Durant N, et al. Perceived weight discrimination in the CARDIA study: differences by race, sex, and weight status. Obes Silver Spring Md. 2014;22(2):530-536. https://doi.org/10.1002/oby.20438

50. Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obes Silver Spring Md. 2009;17(5):941-964. https://doi.org/10.1038/oby.2008.636

51. Lawrence BJ, Kerr D, Pollard CM, et al. Weight bias among health care professionals: A systematic review and meta-analysis. Obesity. 2021;29(11):1802-1812. https://doi.org/10.1002/oby.23266

52. Shields AT. Examination of the obesity epidemic from a behavioral perspective. Int J Behav Consult Ther. 2009;5(1):142. https://files.eric.ed.gov/fulltext/EJ861357.pdf

53. Skinner BF. Sobre el conductismo. Barcelona: Fontanella; 1977. https://desarmandolacultura.wordpress.com/wp-content/uploads/2018/04/skinner-b-f-sobre-el-conductismo.pdf

54. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. The Lancet. 2011; 378 (9793): 804-814. https://doi.org/10.1016/S0140-6736(11)60813-1

55. Javed Z, Valero-Elizondo J, Maqsood MH, et al. Social determinants of health and obesity: Findings from a national study of US adults. Obes Silver Spring Md. 2022;30(2): 491-502. https://doi.org/10.1002/oby.23336

56. Oficina de Análisis y Prospección de Navarra. Determinantes Sociales de La Salud En Navarra: La Influencia Del Sexo, La Edad, El País de Nacimiento, Los Ingresos y La Renta Garantizada. Departamento de Presidencia e Igualdad del Gobierno de Navarra.; 2023. https://www.observatoriorealidadsocial.es/es/estudios/determinantes-sociales-de-la-salud-en-navarra-la-influencia-del-sexo-la-edad-el-pais-de-nacimiento-los-ingresos-y-la-renta-garantizada/es-589600/

57. Luli M, Yeo G, Farrell E, et al. The implications of defining obesity as a disease: a report from the Association for the Study of Obesity 2021 annual conference. eClinicalMedicine. 2023;58. https://doi.org/10.1016/j.eclinm.2023.101962

58. Vallgårda S, Nielsen MEJ, Hansen AKK, et al. Should Europe follow the US and declare obesity a disease?: a discussion of the so-called utilitarian argument. Eur J Clin Nutr. 2017;71(11):1263-1267. https://doi.org/10.1038/ejcn.2017.103

59. Rathbone JA, Cruwys T, Jetten J, Banas K, Smyth L, Murray K. How conceptualizing obesity as a disease affects beliefs about weight, and associated weight stigma and clinical decision-making in health care. Br J Health Psychol. 2023; 28(2):291-305. https://doi.org/10.1111/bjhp.12625

60. Gilmore AB, Fabbri A, Baum F, et al. Defining and conceptualising the commercial determinants of health. The Lancet. 2023; 401(10383): 1194-1213. https://doi.org/10.1016/S0140-6736(23)00013-2

61. Terhune C, Respaut R. Maker of Wegovy, Ozempic showers money on U.S. obesity doctors. Reuters. https://www.reuters.com/investigates/special-report/health-obesity-novonordisk-doctors/. Published December 1, 2023.

62. Haseeb M, Chhatwal J, Xiao J, Jirapinyo P, Thompson CC. Semaglutide vs Endoscopic Sleeve Gastroplasty for Weight Loss. JAMA Netw Open. 2024;7(4):e246221-e246221. https://doi.org/10.1001/jamanetworkopen.2024.6221

63. Mozaffarian D. GLP-1 Agonists for Obesity—A New Recipe for Success? JAMA. Published online February 29, 2024. https://doi.org/10.1001/jama.2024.2252

64. Semaglutide for managing overweight and obesity. NICE. Published online September 4, 2023. Accessed March 13, 2024. https://www.nice.org.uk/guidance/ta875

65. Martín Fernández-Gallardo A. La red oscura que las multinacionales farmacéuticas ocultan tras los pagos a profesionales sanitarios: sus líderes de opinión en el SNS y su red de intereses al descubierto. Asociación Acceso Justo al Medicamento. Published June 6, 2024. https://accesojustomedicamento.org/la-red-oscura-que-las-multinacionales-farmaceuticas-ocultan-tras-los-pagos-a-profesionales-sanitarios-sus-lideres-de-opinion-en-el-sns-y-su-red-de-intereses-al-descubierto/

66. Oliver T Mytton, Vicky Head, Ian Reckless. Public health perspective on new weight loss medications. BMJ. 2024;384: q196. https://doi.org/10.1136/bmj.q196

67. Han SH, Ockerman K, Furnas H, et al. Practice Patterns and Perspectives of the Off-Label Use of GLP-1 Agonists for Cosmetic Weight Loss. Aesthet Surg J. Published online December 12, 2023:sjad364. https://doi.org/10.1093/asj/sjad364

68. Tudor Hart J. THE INVERSE CARE LAW. The Lancet. 1971; 297 (7696): 405-412. https://doi.org/10.1016/S0140-6736(71)92410-X

69. Golden NH, Schneider M, Wood C, et al. Preventing Obesity and Eating Disorders in Adolescents. Pediatrics. 2016; 138(3):e20161649. https://doi.org/10.1542/peds.2016-1649

70. Wu J, Liu J, Li S, Ma H, Wang Y. Trends in the prevalence and disability-adjusted life years of eating disorders from 1990 to 2017: results from the Global Burden of Disease Study 2017. Epidemiol Psychiatr Sci. 2020;29:e191. https://doi.org/10.1017/S2045796020001055

71. Melissa M Lane, Elizabeth Gamage, Shutong Du, et al. Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. BMJ. 2024; 384:e077310. https://doi.org/10.1136/bmj-2023-077310

72. McKinlay John B. A Case for Refocusing Upstream: The Political Economy of Illness. Article presented at: Applying Behavioral Science to Cardiovascular Risk, American Heart Association; 1975. Seattle, WA. Reprinted in: IAPHS Occasional Classics, 2019. https://iaphs.org/wp-content/uploads/2019/11/IAPHS-McKinlay-Article.pdf

Servicio Navarro de Salud
Osasunbidea

ISSN
1138-1043

INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
sinfomed@navarra.es

Web site
www.bit.navarra.es