ORIGINAL RESEARCH

Comparison of the Efficacy of Anti-Obesity Medications in Real-World Practice

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Purpose: Anti-obesity medications (AOMs), along with lifestyle interventions, are effective means of inducing and maintaining weight loss in patients with obesity. Although the efficacy of AOMs has been reported, there have been no direct comparisons of these drugs. Therefore, in the present study, we aimed to compare the efficacy of all the AOMs available in Korea in a real-world setting.
Patients and Methods: The body weight and composition of 205 adults treated with phentermine, phentermine/topiramate, liraglutide, naltrexone/bupropion, lorcaserin, or orlistat for at least 6 months were analyzed at 2 month intervals. The prevalence of the achievement of a ≥5% weight loss and the changes in body composition were compared between participants using each AOM at each visit.
Results: A total of 132 (64.4%) participants achieved ≥5% weight loss within 6 months (prevalence of ≥5% weight loss after 6 months: phentermine, 87.2%; phentermine/topiramate, 67.7%; liraglutide, 58.1%; naltrexone/bupropion, 35.3%; lorcaserin, 75%; orlistat, 50%). At each visit, after adjustment for age, sex, and baseline body weight, phentermine use was associated with a significantly higher prevalence of ≥5% weight loss than the use of the other AOMs, except for liraglutide. There were significant differences in the body weight, body mass index and body fat mass among the AOM groups by visit (P for interaction <0.05), but not in their waist circumference, skeletal muscle mass, percentage body fat, or visceral fat area.
Conclusion: All the AOMs were effective at inducing and maintaining weight loss, in the absence of significant changes in muscle mass, over a 6 month period, and the short-term use of phentermine and the long-term use of phentermine/topiramate or liraglutide would be practical choices for the treatment of obesity. However, further, large-scale studies are necessary to confirm these findings.
Keywords: anti-obesity medication, body composition, weight loss, body weight maintenance, obesity

Introduction

Obesity is a chronic condition that predisposes toward and exacerbates a range of diseases, including type 2 diabetes mellitus, cardiovascular disease, stroke, peripheral vascular disease, sleep apnea, fatty liver disease, osteoarthritis, infertility, depression, anxiety, and types of cancer.[1] Decades have passed since the World Health Organization (WHO) defined obesity as the "new epidemic of the 21st century" and emphasized that obesity should be managed as a chronic disease.[2] However, the number of people with obesity continues to increase worldwide,[3] and South Korea is no exception. In Korea, the prevalence of obesity significantly increased by 1.18-fold over the decade from 2009, from 32.6% to 38.5%, using a definition of a body mass index (BMI) ≥ 25 kg/m², in accordance with the Asia-Pacific World Health Organization (WHO) criteria.[4,5] Obesity not only represents a health problem for individuals, but also a substantial public health issue and economic burden. Therefore, it is essential to identify effective treatments.

A loss of body weight of 3–5% has been shown to reduce blood glucose concentration, improve quality of life, and reduce the risk of cardiovascular disease; and a 5–10% weight loss over 6 months has been recommended as an initial goal to achieve health benefits.[6,7] Lifestyle interventions, including dietary, exercise, and behavioral modifications, are the key methods of achieving weight loss. In addition, pharmacologic interventions should be considered for patients living with obesity or those who are overweight with obesity-related comorbidities, particularly if they are unable to

achieve weight loss through lifestyle interventions alone.[8] Weight loss and long-term weight maintenance are essential for the successful treatment of obesity. However, it has been reported that approximately 80% of people who achieve a weight loss of ≥10% are not successful at maintaining their weight loss over a period of 1 year.[9] Interestingly, a meta-analysis showed no difference in the maintenance of weight loss between a group that lost weight through diet and exercise, and another group that was administered pharmacologic treatment alongside these until 6 months had passed since the initial weight loss. However, after 24 months, the weight loss was better maintained in the latter group.[10]

In response to weight loss and a reduction in total energy intake, metabolic adaptation occurs, with an increase in the secretion of appetite-stimulating hormones and a decrease in the secretion of appetite-suppressing hormones, resulting in lower basal metabolic rate (BMR) and a tendency toward weight regain.[11] Therefore, the aims of the treatment of obesity should be to reduce body fat mass (BFM) but not fat-free mass (FFM), to minimize this reduction in BMR and prevent weight regain.[12] To this end, it is important to carefully monitor changes in body composition, to provide treatment that is tailored to the change in weight loss in each patient, to manage their comorbidities, and to adopt strategies for the long-term maintenance of the weight loss.

A few studies have investigated the effectiveness of Anti-Obesity Medications (AOMs) in real-world settings. However, direct comparisons of the efficacies of these medications within Korean populations have yet to be conducted. Therefore, in the present study, we aimed to compare the effects of all the AOMs available in Korea in patients who underwent treatment for their obesity, to identify which are effective for long-term weight loss in such patients.

Materials and Methods
Participants and Methods

Obesity and overweight were defined according to the Asia-Pacific WHO criteria, using a BMI of ≥25.0 kg/m^2 for obesity and 23.0–24.9 kg/m^2 for overweight.[4] We enrolled adults aged 19–65 years who had obesity or overweight with obesity-related comorbidities, who were prescribed AOMs by two family medicine specialists at the obesity clinics of Kyungpook National University Hospital and Kyungpook National University Chilgok Hospital between March 2015 and December 2020. This retrospective study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (protocol no. KNUCH 2021–08-047). Considering the retrospective design of the current study and determining that a waiver of informed consent would not compromise the rights and welfare of the subjects, the institutional ethics committee approved the waiver of the requirement for informed consent. To ensure the anonymity and confidentiality of patients' data, only data essential to the study was extracted from medical records, access to the data was restricted, and identifiers were eliminated. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

We retrospectively reviewed the medical records of patients who were administered a single AOM for at least 6 months, and underwent weight measurement and a complete body composition analysis during their first visit. Clinical data were collected at the 2 month (8 ± 2 weeks), 4 month (16 ± 2 weeks), and 6 month (24 ± 2 weeks) time points during the administration of the medications.

The exclusion criteria were as follows: i) gastrointestinal surgery, including bariatric surgery before or during the period of medication; ii) use of AOMs, herbal medicines, or supplementary medicines that could have affected body weight within the preceding 3 months; iii) malignancy detected within the year prior to the commencement of medication; iv) failure to take medications regularly, owing to serious adverse reactions, poor compliance, or hospital visits; v) a change in the AOM administered or the use of a combination of AOMs; vi) insufficient data regarding body weight and body composition at the start of the period of medication and 2, 4, and 6 months following the commencement; vii) serious cardiovascular disease, including angina pectoris, myocardial infarction, heart failure, transient ischemic attack, and ischemic stroke, within the preceding year; and viii) unintentional loss of ≥5% of basal body weight within the 3 months prior to a hospital visit.

Anti-Obesity Medications

The six AOMs available in Korea, phentermine, phentermine/topiramate, liraglutide, naltrexone/bupropion, lorcaserin, and orlistat, were compared. In 2023, all six AOMs were approved in Korea for the treatment of obesity, with the

exception of lorcaserin, which was used between February 2015 and February 2020, but was withdrawn by the Food and Drug Administration (FDA) because of an associated increase in the risk of developing tumors.

The physicians in the obesity clinics had selected an AOM to administer to each participant on the basis of the results of laboratory testing (liver enzymes, indices of kidney function, and thyroid hormone concentrations), their underlying diseases, their history of medication, their family history, their dietary habits and lifestyle, and their individual preferences. The dose of each AOM was gradually and individually adjusted according to the participant's baseline body weight, their response to the medication, any adverse reactions, safety, affordability, and the participant's preferences, starting from the lowest dose, and increasing the dose until the patient achieved a significant weight-loss effect without any discomfort. The maximum dose for each AOM was as follows: phentermine 37.5 mg/day, phentermine/topiramate 15/92 mg/day, liraglutide 3 mg/day, naltrexone/bupropion 32/360 mg/day, lorcaserin 20 mg/day, and orlistat 360 mg/day.

Lifestyle Interventions

The physicians in the obesity clinics prescribed a high-intensity lifestyle intervention that comprised dietary, exercise, and behavioral modifications for all of the participants at each visit. The dietary intervention consisted of a well-balanced, low-calorie diet comprising 55–60% carbohydrates, 15–20% protein, and 20–25% fat. An intake of 1.2–1.5 g protein per kg of body weight was recommended to minimize the loss of fat-free mass.[13–16] In addition, a reduction in calorie intake of approximately 500–1000 kcal/day from the recommended energy requirements (1200–1500 kcal/day for women and 1500–1800 kcal/day for men) was stipulated.[6] Counseling regarding the most appropriate diet for weight loss was conducted by a nutritionist following a request by a participant or physician. Both aerobic and anaerobic exercises were strongly recommended to each of the participants. The performance of moderate-intensity aerobic exercise for 30–50 min spread over 3–5 times/week and resistance exercise 2–3 times/week was recommended. For patients with musculoskeletal disease or disability, a consultation with a rehabilitation medicine specialist was conducted to devise an appropriate exercise regimen. In addition to exercise, participants were also encouraged to increase their daily non-exercise physical activity, such as by choosing to walk instead of driving, parking cars further away from their destination, using a pedometer, engaging in household activities that involve movement, playing with pets, dancing, and window-shopping. A reduction in sitting time was also recommended as an effective way of increasing non-exercise physical activity; for example, by standing while working, using a standing desk or adjustable desk converter, taking regular breaks, and using stairs instead of elevators.

Demographic Characteristics

The medical history of the participants connected with their first visit was obtained through a review of medical records. The presence of underlying comorbidities, such as hypertension, diabetes, dyslipidemia, psychiatric disorders, thyroid disease, sleep apnea, fatty liver disease, obesity-related arthritis, and gout; any pre-existing medication; smoking status; alcohol consumption; and exercise status were recorded. Those with underlying comorbidities were defined as those who had been previously diagnosed with such a condition or who were taking appropriate medication. The alcohol consumption of each participant per week was calculated using the number of standard drinks consumed of 14 g alcohol. Those who consumed more than the recommended maximum (eight drinks/week for men and four drinks/week for women) were classified as drinkers, and those who drank less than the recommended maximum were classified as non-drinkers.[17] Current smoking is defined as the use of tobacco products and associated substances, including cigarettes, cigars, pipes, and e-cigarettes. Regular exercise was defined as moderate-to-high intensity exercise performed for ≥ 150 minutes per week.[18]

Measurement of Obesity-Related Parameters

At the beginning of the treatment period and during each visit, the height and body weight of each participant were measured using an automatic height-weight scale (GL-150RP, G-Tech International, Gyeonggi-do, Korea). BMI was calculated by dividing the body weight (kg) of the participants by the square of their height (m). Height was measured with the back and heels of the participant against the wall and their feet 60° apart, while they took a deep breath. Waist circumference (WC) was measured twice at the midpoint between the top of the iliac crest and the bottom of the lowest

rib, while the participant was standing with their feet 25–30 cm apart and exhaling normally, and the mean value was used in subsequent analyses.

The body composition of the participants was analyzed with an Inbody 770 (Inbody, Seoul, Korea) using the bioelectric impedance analysis (BIA) method. Tactile electrodes were placed at eight precise points on the body and weak alternating currents of six different frequencies (1, 5, 50, 250, 500, and 1000 kHz) were sent to the limbs. The generated impedance was used in the subsequent analyses. According to the manufacturer's instructions, and to reduce the error caused by the amount of water in the body, the use of alcohol or diuretics was avoided prior to this procedure, and beverages were not consumed during the hour immediately preceding the assessment. The measurement was performed while the participant was standing barefoot, wearing light clothing, and maintaining the recommended posture. Skeletal muscle mass (SMM), body fat mass (BFM), percentage body fat (PBF), and visceral fat area (VFA) were determined. The values of these parameters at the start of the intervention, and after 2, 4, and 6 months of the intervention were compared for each AOM.

Primary and Secondary Outcomes

The primary outcome of the study was the achievement of a weight loss of ≥5% within 6 months of starting the administration of each AOM. The secondary outcomes were the achievement of a weight loss of ≥10% within 6 months, and the changes in body weight, WC, and body composition (SMM, BFM, PBF, and VFA).

Statistical Analysis

Pearson's chi-square test, Fisher's exact test (categorical data), and Kruskal–Wallis test (continuous data) were used to compare the general characteristics of each AOM group. Logistic regression, adjusted for age, sex, and baseline body weight, was performed to compare the prevalence of the achievement of a weight loss of ≥5% at each time point during the administration of each AOM. In addition, repeated-measures ANOVA, adjusted for age, sex, and baseline body weight, was used to compare obesity-related parameters at each time point, and *post-hoc* testing was performed using the Bonferroni method. Statistical significance was accepted at $p < 0.05$, and all statistical analyses were performed using SPSS version 25.0 (IBM Inc., Armonk, NY, USA).

Results

General Characteristics of the Participants

Of the 615 individuals who were prescribed an AOM within the study period, 410 were excluded because they fulfilled one of the exclusion criteria (209 who were lost to follow-up within 6 months, 95 who did not take their medication regularly, 32 who changed to another AOM or were administered another combination of AOMs, 28 who underwent gastrointestinal surgery, and 46 for other reasons); therefore, the remaining 205 were selected as participants (Figure 1).

The mean age of the 205 participants was 39.3 years and 71.2% were female. Their mean BMI was 34.6 ± 7.98 kg/m^2, indicative of morbid obesity. Phentermine was administered to 39 (19.0%) participants, phentermine/topiramate to 51 (24.9%), liraglutide to 62 (30.2%), naltrexone/bupropion to 17 (8.3%), lorcaserin to 24 (11.7%), and orlistat to 12 (5.9%). There were significant differences in the age, baseline body weight, BMI, WC, SMM, BFM, PBF, and VFA of the participants among the AOM groups.

The phentermine group had the lowest mean age (34.00 ± 10.35 years) and the phentermine/topiramate group had the highest mean age (42.47 ± 12.64 years). The phentermine group had the highest BMI (38.84 ± 9.16 kg/m^2) and the orlistat group had the lowest BMI (32.74 ± 8.74 kg/m^2). The phentermine group had the largest WC (116.54 ± 18.68 cm) and the liraglutide group had the smallest WC (103.97 ± 16.39 cm). In addition, the phentermine group had the highest baseline body weight, BFM, PBF, and VFA, and the lorcaserin group had the highest SMM, followed by the phentermine group. The liraglutide group had the lowest SMM (27.22 ± 6.66 kg). There were no significant differences in other demographic characteristics of the participants in the AOM groups, including in the prevalence of their comorbidities (Table 1).
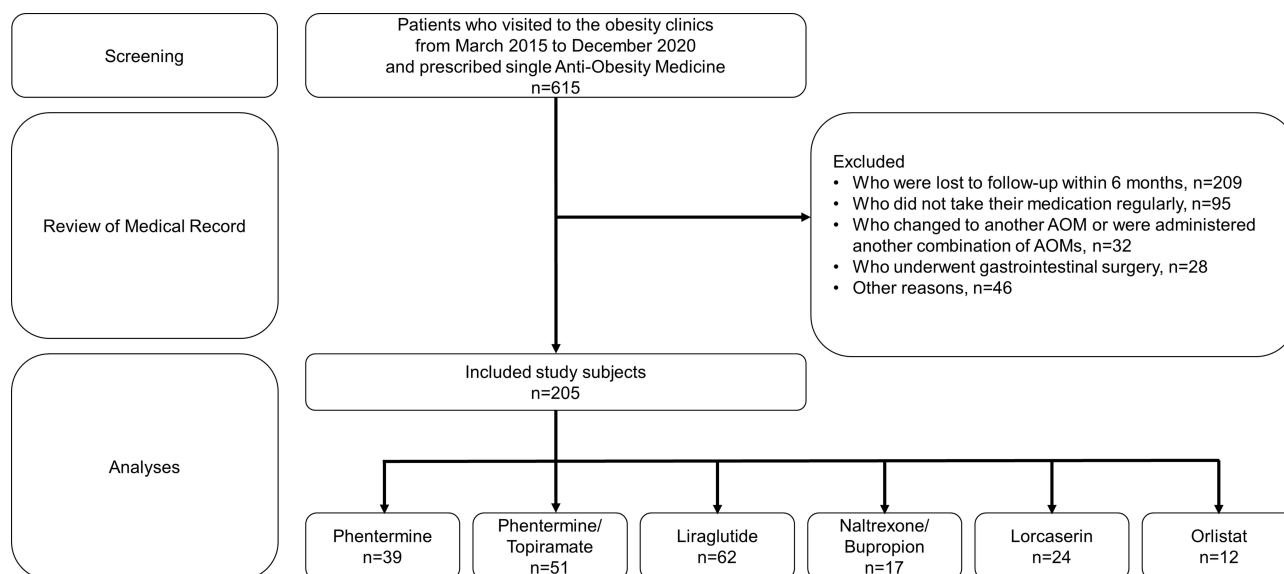
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Figure 1 Study Enrolment. Inclusion and exclusion process.

Primary Outcome: Prevalence of the Achievement of a Weight Loss of ≥5%

A total of 132 (64.4%) of the 205 participants achieved a weight loss of ≥5% during the 6 month study period. The prevalence of a weight loss of ≥5% from baseline was 87.2% for the phentermine group, 75% for the lorcaserin group,

Table 1 Characteristics of the Enrolled Patients Before They Commenced the Use of Anti-Obesity Medication

	Phentermine (n = 39)	Phentermine/ Topiramate (n = 51)	Liraglutide (n = 62)	Naltrexone/ Bupropion (n = 17)	Lorcaserin (n = 24)	Orlistat (n = 12)	*P* value*
Age (years)	34.0 ± 10.4	42.5 ± 12.6	38.7 ± 13.9	41.6 ± 13.6	41.5 ± 9.4	38.6 ± 12.7	0.035
Female	26 (66.7)	38 (74.5)	47 (75.8)	14 (82.4)	13 (54.2)	8 (66.7)	0.321
Height (cm)	166.5 ± 10.1	164.4 ± 10.1	161.9 ± 8.5	163.8 ± 6.9	166.8 ± 9.9	165.1 ± 8.1	0.133
Body weight (kg)	108.5 ± 30.6	93.42 ± 26.03	87.5 ± 22.0	91.0 ± 19.3	94.9 ± 31.4	91.2 ± 34.8	0.015
Body mass index (kg/m^2)	38.8 ± 9.2	34.3 ± 7.9	33.1 ± 6.7	33.9 ± 7.2	33.4 ± 7.6	32.7 ± 8.7	0.018
Waist circumference (cm)	116.5 ± 18.7	107.2 ± 17.1	104.0 ± 16.4	106.1 ± 13.1	105.7 ± 18.0	105.6 ± 20.6	0.029
Skeletal muscle mass (kg)	34.6 ± 11.0	30.6 ± 10.9	27.2 ± 6.7	30.2 ± 9.8	36.4 ± 13.6	33.6 ± 15.4	0.001
Body fat mass (kg)	49.4 ± 18.0	39.5 ± 15.3	37.7 ± 13.4	38.6 ± 8.3	38.3 ± 17.0	37.3 ± 17.9	0.006
Percentage body fat	44.8 ± 6.6	41.5 ± 7.6	42.5 ± 6.9	43.0 ± 4.6	39.8 ± 5.0	40.2 ± 5.0	0.041
Visceral fat area (cm^2)	211.1 ± 58.7	179.3 ± 56.9	177.3 ± 53.9	186.5 ± 37.2	163.5 ± 47.6	171.0 ± 49.3	0.013
Hypertension	20 (51.3)	17 (33.3)	19 (30.6)	5 (29.4)	6 (25)	5 (41.7)	0.249
Type 2 diabetes	6 (15.4)	13 (25.5)	10 (16.1)	0 (0)	4 (16.7)	2 (16.7)	0.424†
Dyslipidemia	10 (25.6)	16 (31.4)	17 (27.4)	4 (23.5)	7 (29.2)	4 (33.3)	0.980
Psychiatric disorders	7 (17.9)	4 (7.8)	16 (25.8)	2 (11.8)	2 (8.3)	2 (16.7)	0.690†
Thyroid disease	1 (11.8)	5 (9.8)	7 (11.3)	2 (11.8)	4 (16.7)	1 (8.3)	0.230†
Sleep apnea	10 (25.6)	14 (27.5)	7 (11.3)	1 (5.9)	1 (4.2)	1 (8.3)	0.392†
Fatty liver	10 (25.6)	22 (43.1)	14 (22.6)	5 (29.4)	12 (50.0)	5 (41.7)	0.076
Arthropathy	12 (30.8)	18 (35.3)	21 (33.9)	6 (35.3)	9 (37.5)	5 (41.7)	0.986
Gout	2 (5.1)	4 (7.8)	3 (4.8)	0 (0)	3 (12.5)	0 (0)	0.127†
Alcohol consumer‡	14 (35.9)	18 (35.3)	17 (27.4)	2 (11.8)	6 (25.0)	6 (50.0)	0.249
Current smoker	9 (23.1)	10 (19.6)	11 (17.7)	2 (11.8)	5 (20.8)	3 (25.0)	0.876†
Regular exercise	19 (48.7)	26 (51.0)	42 (67.7)	12 (70.6)	19 (79.2)	8 (66.7)	0.076

Notes: Data are presented as mean ± standard deviation or number of patients (%). *Pearson's chi-square test for discrete variables and Kruskal–Wallis test for continuous variables. †Fisher's exact test. ‡Participants who consumed ≥8 drinks/week (men) or ≥4 drinks/week (women) (1 drink =14 g of alcohol).

67.7% for the phentermine/topiramate group, 58.1% for the liraglutide group, 50% for the orlistat group, and 35.3% for the naltrexone/bupropion group (P = 0.002) (Figure 2).

The odds ratios (ORs) of a weight loss of ≥5% for each AOM group were calculated at each time point during the intervention period, with the phentermine group being used as the reference, after adjustment for age, sex, and baseline body weight. Two months after the start of the intervention, the OR for the lorcaserin group was 0.228 (95% confidence interval [CI], 0.090–0.579) and the OR for the orlistat group was 0.328 (95% CI, 0.130–0.831), which implies that early after the initiation of the AOMs, less marked weight loss was associated with lorcaserin and orlistat administration than with phentermine administration. At the 4 month time point, the OR of the naltrexone/bupropion group was 0.178 (95% CI, 0.047–0.671) vs the phentermine group, but none of the other AOMs generated significantly different results. At the 6 month time point, the ORs for each AOM group, compared with the phentermine group, were as follows: phentermine/topiramate, 0.159 (95% CI, 0.036–0.70); naltrexone/bupropion, 0.089 (95% CI, 0.022–0.355); lorcaserin, 0.221 (95% CI, 0.074–0.661); and orlistat, 0.281 (95% CI, 0.092–0.863). The liraglutide group did not significantly differ in the weight loss it induced from the phentermine group at any of the time points assessed (Table 2).

Secondary Outcomes: Prevalence of the Achievement of a Weight loss of ≥10% and the Changes in Body Composition

A total of 62 participants (30.2%) had lost >10% of their baseline body weight after 6 months of AOM: 56.4% of the phentermine group, 35.3% of the phentermine/topiramate group, 33.3% of the lorcaserin group, 25% of the orlistat group, 14.2% of the liraglutide group, and 11.8% of the naltrexone/bupropion group (P <0.001) (Figure 3).

The changes in body weight, BMI, WC, and body composition at 2 month intervals from the start of the intervention were compared across the AOM groups after adjustment for age, sex, and baseline body weight. There were significant differences in the body weight (kg, %), BMI and BFM of the AOM groups at each time point following the initiation of treatment (P for interaction <0.05). However, there were no significant differences in WC, SMM, PBF or VFA between the AOM groups (Figure 4).
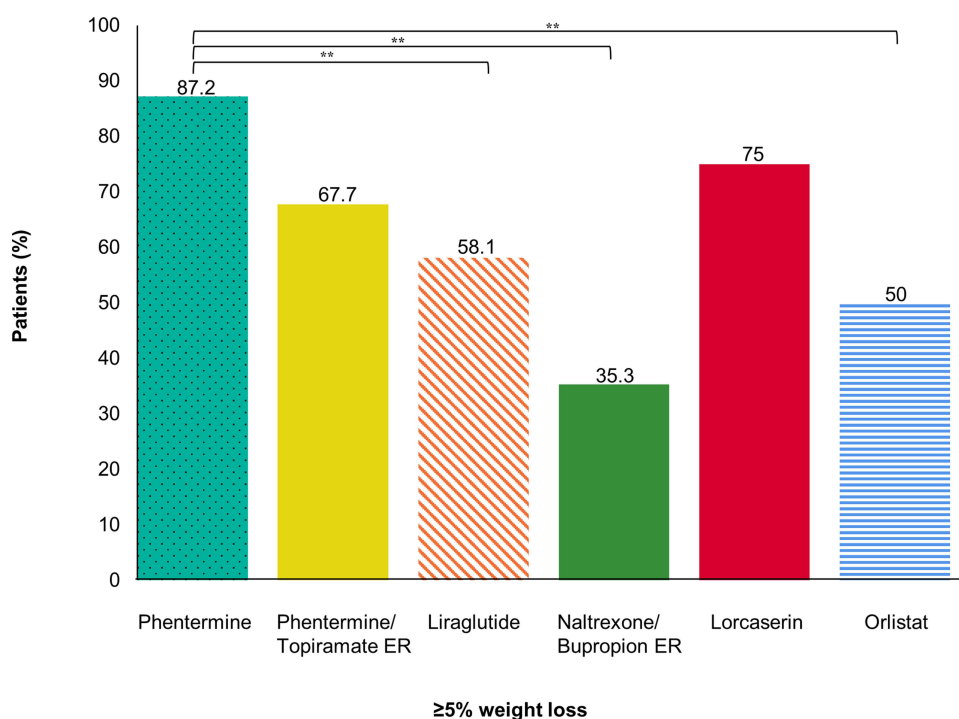

Figure 2 Prevalences of the achievement of ≥5% weight loss during 6 months of administering anti-obesity medications.
Notes: Pearson's Chi-square test and Bonferroni correction for multiple comparisons. ** P < 0.01.

Table 2 Adjusted Odds Ratio for the Achievement of a ≥ 5% Weight Loss at Each Visit

	Phentermine	Phentermine/ Topiramate	Liraglutide	Naltrexone/ Bupropion	Lorcaserin	Orlistat
	Odds ratio (95% Confidence Interval)					
5% Weight loss after 2 months	Reference	0.335 (0.076−1.473)	0.970 (0.330−2.849)	0.283 (0.076−1.053)	0.228 (0.090−0.579)	0.328 (0.130−0.831)
5% Weight loss after 4 months	Reference	0.638 (0.164−2.480)	1.780 (0.558−5.676)	0.178 (0.047−0.671)	0.539 (0.224−1.296)	0.761 (0.307−1.884)
5% Weight loss after 6 months	Reference	0.159 (0.036−0.709)	0.503 (0.131−1.941)	0.089 (0.022−0.355)	0.221 (0.074−0.661)	0.281 (0.092−0.863)

Notes: The logistic regression analysis was adjusted for age, sex, and baseline body weight.

Discussion

Obesity is associated with a wide range of diseases, poor quality of life, and an increase in overall mortality, both direct and indirect.[1,19] The management of obesity should be comprehensive and continuous to facilitate both weight loss and maintenance. The management of obesity involves a combination of lifestyle change, behavioral modification, and medical intervention. Lifestyle management is fundamental and should be prioritized,[8] but it is challenging to adhere to intensive lifestyle interventions for a prolonged period of time. Indeed, most patients with obesity fail to achieve significant weight loss using lifestyle interventions alone.[20] Even after significant weight loss, approximately one-third and >80% of patients regain their lost weight after 1 and 5 years, respectively.[21] However, the use of a pharmacological treatment alongside dietary/lifestyle interventions is associated with superior weight loss and longer weight maintenance than lifestyle interventions alone.[10,22]

Despite the proven efficacy of AOMs in several studies, there is a lack of direct, head-to-head comparisons of their effectiveness. Additional clinical outcomes derived from comparing the efficacy of AOMs using real-world data remain valuable. They contribute to our understanding of the drugs' utility and are beneficial for clinical decision-making in
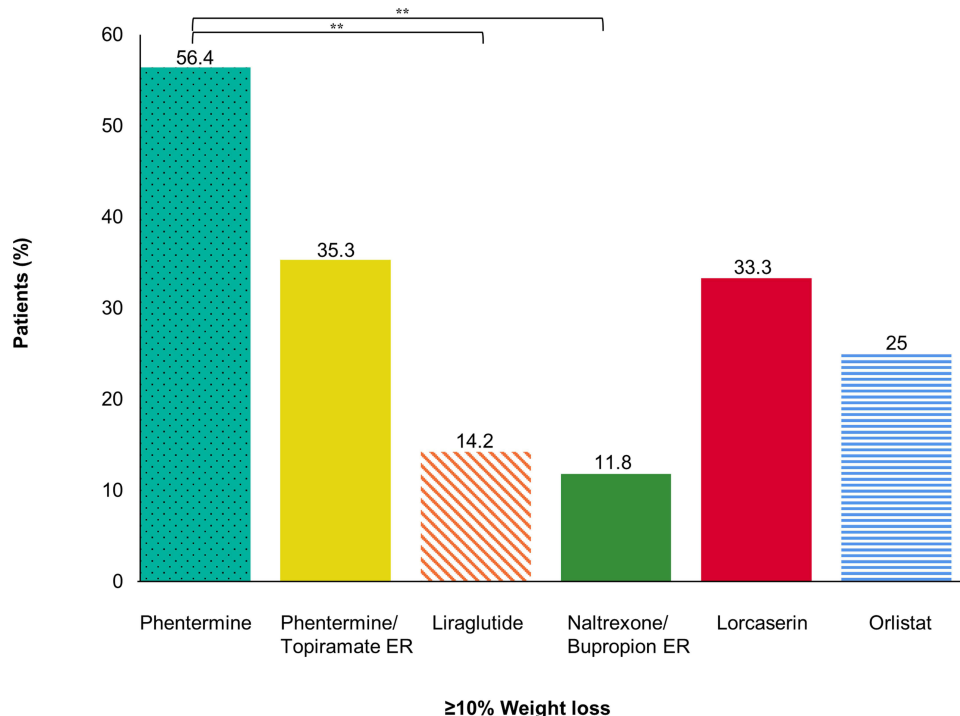
Figure 3 Prevalences of the achievement of ≥10% weight loss during 6 months of administering anti-obesity medications.
Notes: Pearson's Chi-square test and Bonferroni correction for multiple comparisons. ** P < 0.01.
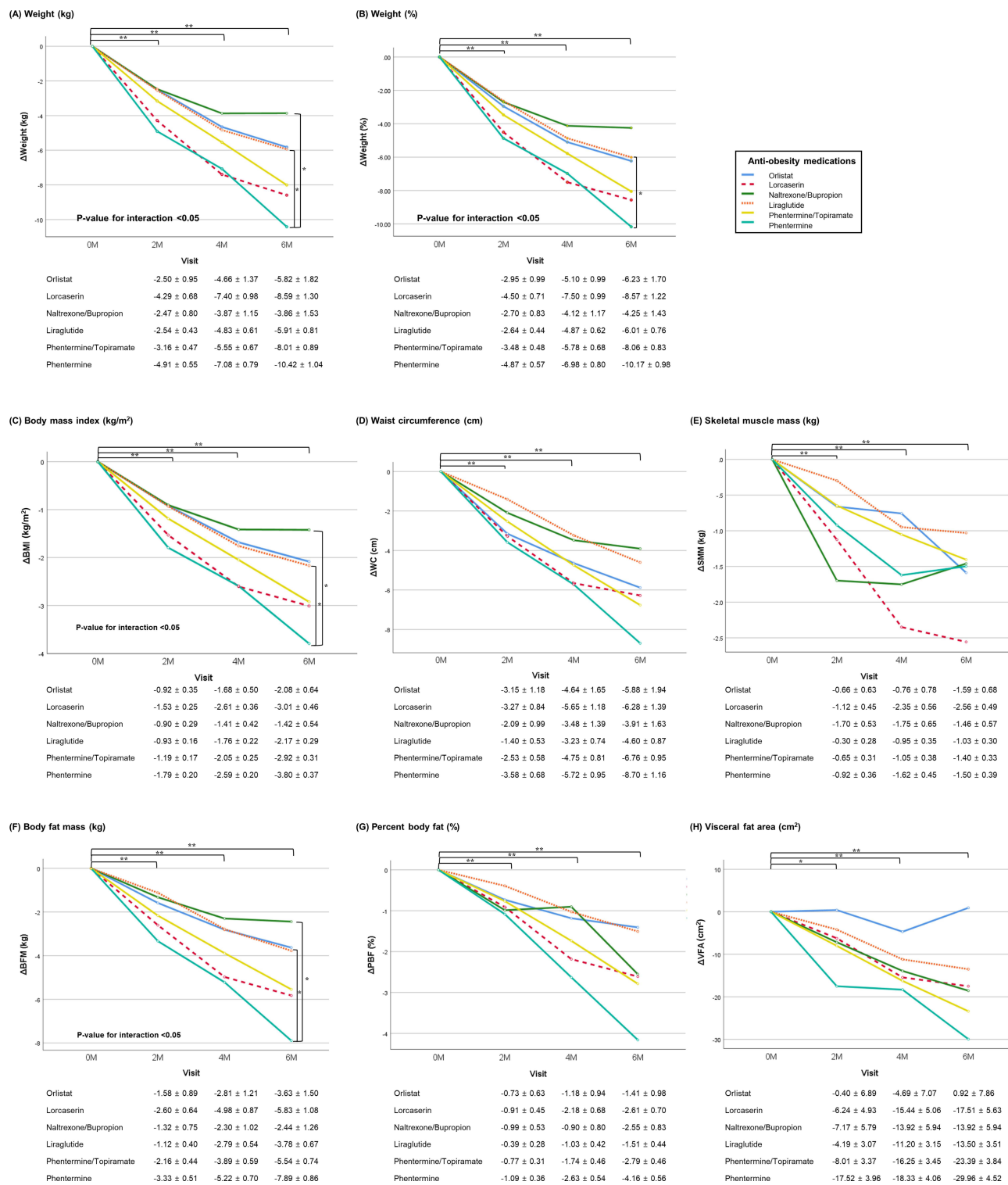
(A) Weight (kg)

Orlistat	-2.50 ± 0.95	-4.66 ± 1.37	-5.82 ± 1.82
Lorcaserin	-4.29 ± 0.68	-7.40 ± 0.98	-8.59 ± 1.30
Naltrexone/Bupropion	-2.47 ± 0.80	-3.87 ± 1.15	-3.86 ± 1.53
Liraglutide	-2.54 ± 0.43	-4.83 ± 0.61	-5.91 ± 0.81
Phentermine/Topiramate	-3.16 ± 0.47	-5.55 ± 0.67	-8.01 ± 0.89
Phentermine	-4.91 ± 0.55	-7.08 ± 0.79	-10.42 ± 1.04

(B) Weight (%)

Orlistat	-2.95 ± 0.99	-5.10 ± 0.99	-6.23 ± 1.70
Lorcaserin	-4.50 ± 0.71	-7.50 ± 0.99	-8.57 ± 1.22
Naltrexone/Bupropion	-2.70 ± 0.83	-4.12 ± 1.17	-4.25 ± 1.43
Liraglutide	-2.64 ± 0.44	-4.87 ± 0.62	-6.01 ± 0.76
Phentermine/Topiramate	-3.48 ± 0.48	-5.78 ± 0.68	-8.06 ± 0.83
Phentermine	-4.87 ± 0.57	-6.98 ± 0.80	-10.17 ± 0.98

Anti-obesity medications
- Orlistat
- Lorcaserin
- Naltrexone/Bupropion
- Liraglutide
- Phentermine/Topiramate
- Phentermine

(C) Body mass index (kg/m²)

Orlistat	-0.92 ± 0.35	-1.68 ± 0.50	-2.08 ± 0.64
Lorcaserin	-1.53 ± 0.25	-2.61 ± 0.36	-3.01 ± 0.46
Naltrexone/Bupropion	-0.90 ± 0.29	-1.41 ± 0.42	-1.42 ± 0.54
Liraglutide	-0.93 ± 0.16	-1.76 ± 0.22	-2.17 ± 0.29
Phentermine/Topiramate	-1.19 ± 0.17	-2.05 ± 0.25	-2.92 ± 0.31
Phentermine	-1.79 ± 0.20	-2.59 ± 0.20	-3.80 ± 0.37

(D) Waist circumference (cm)

Orlistat	-3.15 ± 1.18	-4.64 ± 1.65	-5.88 ± 1.94
Lorcaserin	-3.27 ± 0.84	-5.65 ± 1.18	-6.28 ± 1.39
Naltrexone/Bupropion	-2.09 ± 0.99	-3.48 ± 1.39	-3.91 ± 1.63
Liraglutide	-1.40 ± 0.53	-3.23 ± 0.74	-4.60 ± 0.87
Phentermine/Topiramate	-2.53 ± 0.58	-4.75 ± 0.81	-6.76 ± 0.95
Phentermine	-3.58 ± 0.68	-5.72 ± 0.95	-8.70 ± 1.16

(E) Skeletal muscle mass (kg)

Orlistat	-0.66 ± 0.63	-0.76 ± 0.78	-1.59 ± 0.68
Lorcaserin	-1.12 ± 0.45	-2.35 ± 0.56	-2.56 ± 0.49
Naltrexone/Bupropion	-1.70 ± 0.53	-1.75 ± 0.65	-1.46 ± 0.57
Liraglutide	-0.30 ± 0.28	-0.95 ± 0.35	-1.03 ± 0.30
Phentermine/Topiramate	-0.65 ± 0.31	-1.05 ± 0.38	-1.40 ± 0.33
Phentermine	-0.92 ± 0.36	-1.62 ± 0.45	-1.50 ± 0.39

(F) Body fat mass (kg)

Orlistat	-1.58 ± 0.89	-2.81 ± 1.21	-3.63 ± 1.50
Lorcaserin	-2.60 ± 0.64	-4.98 ± 0.87	-5.83 ± 1.08
Naltrexone/Bupropion	-1.32 ± 0.75	-2.30 ± 1.02	-2.44 ± 1.26
Liraglutide	-1.12 ± 0.40	-2.79 ± 0.54	-3.78 ± 0.67
Phentermine/Topiramate	-2.16 ± 0.44	-3.89 ± 0.59	-5.54 ± 0.74
Phentermine	-3.33 ± 0.51	-5.22 ± 0.70	-7.89 ± 0.86

(G) Percent body fat (%)

Orlistat	-0.73 ± 0.63	-1.18 ± 0.94	-1.41 ± 0.98
Lorcaserin	-0.91 ± 0.45	-2.18 ± 0.68	-2.61 ± 0.70
Naltrexone/Bupropion	-7.17 ± 5.79	-13.92 ± 5.94	-13.92 ± 5.94
Liraglutide	-0.39 ± 0.28	-1.03 ± 0.42	-1.51 ± 0.44
Phentermine/Topiramate	-0.77 ± 0.31	-1.74 ± 0.46	-2.79 ± 0.46
Phentermine	-1.09 ± 0.36	-2.63 ± 0.54	-4.16 ± 0.56

(H) Visceral fat area (cm²)

Orlistat	-0.40 ± 6.89	-4.69 ± 7.07	0.92 ± 7.86
Lorcaserin	-6.24 ± 4.93	-15.44 ± 5.06	-17.51 ± 5.63
Naltrexone/Bupropion	-7.17 ± 5.79	-13.92 ± 5.94	-13.92 ± 5.94
Liraglutide	-4.19 ± 3.07	-11.20 ± 3.15	-13.50 ± 3.51
Phentermine/Topiramate	-8.01 ± 3.37	-16.25 ± 3.45	-23.39 ± 3.84
Phentermine	-17.52 ± 3.96	-18.33 ± 4.06	-29.96 ± 4.52

Figure 4 Indices of obesity associated with the use of each anti-obesity medication at each visit.

Notes: Changes in (**A**) Weight (kg), (**B**) Weight (%), (**C**) Body mass index (kg/m²), (**D**) Waist circumference,[6] (**E**) Skeletal muscle mass (kg), (**F**) Body fat mass (kg), (**G**) Percentage body fat (%), and (**H**) Visceral fat area (cm²) were compared using repeated-measures ANOVA, adjusted for age, sex, and baseline body weight. The Bonferroni method was used for post-hoc analysis. Data are presented as estimated mean ± standard error. * $P < 0.05$ and ** $P < 0.001$ on post-hoc analysis.

obesity treatment, as they offer a more comprehensive view of clinical outcomes.[23] In the present study, we compared the efficacy of six AOMs (phentermine, phentermine/topiramate, liraglutide, naltrexone/bupropion, lorcaserin, and orlistat) in a real-world clinical setting in 205 patients. After 6 months of using AOMs, 132 (64.4%) had achieved a loss of ≥5%

of baseline body weight, and 30.2% had achieved a weight loss of ≥10%. The prevalence of the maintenance of losses of ≥5% and ≥10% of baseline body weight differed between the AOM groups, with phentermine being associated with the highest prevalence. At all of the assessed time points during the 6 month study period, the use of phentermine was significantly more likely to result in successful weight loss than the other AOMs, with the exception of liraglutide.

For the AOMs used in this study, the overall prevalence of the achievement of a weight loss of ≥5% 6 months after the commencement of therapy was >35%. This is consistent with the target for a loss of ≥5% body weight of >35% of treated patients, which is one of the criteria used to evaluate the efficacy of AOMs by the FDA.[24] All six AOMs used in the present study met this standard, even though the study period was shorter than the recommended length of randomized controlled trials. The FDA guidelines state that the efficacy of AOMs should be assessed ≥1 year after the start of the intervention, and although the treatment period evaluated in this retrospective study was relatively short, it is meaningful that we were able to analyze the results of 6 months of treatment in a real-world clinical setting, despite the high dropout rate associated with the use of AOMs. Indeed, it is very difficult to maintain the treatment of patients with obesity over a long period of time: 50–70% of patients have been shown to drop out or be lost to follow-up in studies conducted in real-world outpatient settings.[25–27] Because obesity is a chronic disease, physicians in obesity clinics should aim to pursue long-term therapy, taking into account the socioeconomic status, psychological status, obesity status, and comorbidities of patients to achieve significant effects.

The primary outcome of the study was the prevalence of the achievement of a weight loss of ≥5% of baseline body weight. The phentermine group showed superior weight loss to the other AOMs after 2, 4, and 6 months of treatment. Phentermine is a sympathomimetic amine that was approved by the FDA in 1959 for short-term (≤12 weeks) weight management. It suppresses appetite by activating POMC neurons in the arcuate nucleus, which release neurotransmitters such as norepinephrine, dopamine, and serotonin.[28,29] It has been prescribed off-label for more than 12 weeks in clinical settings, owing to its low cost and significant weight-loss effect.[29–31] In a previous study conducted in Mexico, 86.5% of the participants who were treated with phentermine 30 mg achieved a weight loss of ≥5%, and 41.1% achieved a weight loss of ≥10%.[32] Another study in the USA indicated that long-term phentermine monotherapy resulted in significantly greater weight loss than non-phentermine treatment (−10.2% vs −4.1% after 156 weeks), without any changes in blood pressure or heart rate.[33] An additional study in the USA using electronic health record data also demonstrated that long-term continuous (>12 months) phentermine users lost 7.4% more weight than short-term single-episode users 24 months after initiating phentermine.[34] For these reasons, phentermine was likely chosen for patients with morbid obesity to increase the likelihood of achieving substantial weight loss and maintaining it. In the present study, participants who used phentermine for 6 months had the highest body weight of the various AOM groups, with a mean BMI of 38.8 kg/m^2. Moreover, the phentermine group was significantly younger and had higher WC, BFM, PBF, and VFA than the other groups, necessitating more substantial weight loss, and similar results were obtained in the present study: participants taking phentermine lost 10.2% of baseline body weight, with 87.2% achieving a weight loss of ≥5%. These effects were significantly better than those observed with the other AOMs at all assessed time points.

The FDA and the Korean Ministry of Food and Drug Safety (MFDS) approved the short-term (≤12 weeks) use of phentermine for weight management as an adjunct to lifestyle interventions.[28,35] Despite previous studies indicating no increased risk of cardiovascular disease with long-term phentermine use,[32–34] the MFDS guidelines, published in August 2020 under the title "Standard for Safe Use of Medical Narcotic Appetite Suppressants", stipulated that the total usage duration should not exceed 12 weeks due to potential side effects.[35,36] Notably, this study involves the prescription of phentermine for periods exceeding 12 weeks, predating the issuance of the MFDS guidelines. Importantly, participants using phentermine for extended periods were intentionally included to analyze the real-world clinical effects of the AOMs. Furthermore, participants in the phentermine group did not use other psychotropic drugs or appetite suppressants concurrently. They underwent close monitoring by specialists every 2–4 weeks, and no significant adverse effects were reported throughout the study period. Nonetheless, it is important not to dismiss concerns associated with the long-term use of phentermine. Caution should be taken when prescribing this drug, especially to individuals at an elevated risk of substance abuse.

A network meta-analysis study of the differences in the effects of AOMs (orlistat, lorcaserin, naltrexone/bupropion, phentermine/topiramate, and liraglutide) over a long period of time showed that the efficacy of phentermine/topiramate and liraglutide were highest in terms of weight loss,[37] which is not consistent with the results of the present study. In the present study, the efficacy of the drugs following phentermine was in the order lorcaserin, phentermine/topiramate, and

liraglutide. However, after adjustment for age, sex, and baseline body weight, it was liraglutide, orlistat, and then lorcaserin, but without any significant differences in the prevalence of the achievement of ≥5% weight loss over 6 months. Possible explanations for these inconsistent findings are as follows. First, the number of participants in each AOM group was small, reducing the statistical power of the study. Second, even though covariates were adjusted for, the characteristics of each AOM group varied. The phentermine/topiramate group was the oldest group, and the liraglutide group had the lowest SMM. Aging and low muscle mass are associated with a low level of physical activity and a low BMR, which can be associated with sub-optimal obesity management.[38,39] Third, we enrolled participants between March 2015 and December 2020, but phentermine/topiramate was released in Korea in January 2020, and therefore few of the participants used this combination. Moreover, in Korea, liraglutide and phentermine/topiramate are more expensive than phentermine or orlistat. The cost of liraglutide and phentermine/topiramate might result in a high dropout rate and poor adherence to long-term obesity management in real-world clinical settings.[40,41] Finally, unlike in randomized clinical trials that are conducted in relatively healthy adults, the majority of the participants in the present study had underlying diseases and were taking other drugs, including psychiatric medications. This might explain the lack of significant differences between the AOM groups, except with respect to phentermine. Therefore, further studies involving a large number of participants are warranted in real-world outpatient settings.

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 analog) that causes weight loss by delaying gastric emptying, inducing early satiety, and reducing appetite.[42,43] In a randomized controlled study of the use of liraglutide 3.0 mg, the prevalence of the achievement of ≥5% weight loss was 63.2% vs 27.1% for placebo, and the percentages achieving ≥10% weight loss were 33.1% vs 10.6% for placebo.[44] Several previous studies have shown that liraglutide is more effective at inducing weight loss than orlistat or lorcaserin.[37,45,46] In the present study, 58.1% of the liraglutide group achieved ≥5% weight loss, which was a higher rate than those for orlistat and naltrexone/bupropion. Furthermore, the prevalence of the maintenance of weight loss associated with the use of liraglutide at 6 months, after adjustment for covariates, was higher than that for the other AOMs, except for phentermine, although this trend was not statistically significant. However, the prevalence of the achievement of weight loss of ≥10% in the liraglutide group was 14.2%, which was lower than that for the orlistat group. AOMs, including liraglutide, have dose-dependent effects, and liraglutide 3.0 mg/day (the maximum dose) is the approved dose for the treatment of obesity.[44,47] Real-world studies of liraglutide have shown that most patients do not reach the maximum dose, but the total weight loss achieved is comparable in patients who take submaximal doses.[48,49] Because liraglutide is the most expensive of the currently available AOMs in Korea when it is administered at the maximum dose, there is a possibility that the patients in the liraglutide group may have chosen a moderate dose, rather than the maximum daily dose, to ensure weight maintenance over 6 months. Although the prevalence of the achievement of weight loss of ≥10% was lower than that shown in previous studies, the use of liraglutide should be favored for long-term weight loss, given that liraglutide was the only AOM that achieved comparable results to phentermine, after adjustment for covariates, after 2, 4, and 6 months.

Lorcaserin is a selective 5-hydroxytryptamine (serotonin) 2c receptor agonist that induces weight loss by appetite suppression. It stimulates proopiomelanocortin/cocaine- and amphetamine-regulated transcript neurons in the hypothalamus, activating melanocortin 3 and 4 receptors through the binding of α-melanocyte stimulating hormone.[50] Although lorcaserin demonstrated substantial weight-loss efficacy in the present study, second only to phentermine, it is no longer available in Korea because a post-approval 5-year follow-up trial of lorcaserin showed a higher incidence of cancer vs the placebo group, which provoked the FDA and MFDS to request the withdrawal of products containing lorcaserin from the market.[35,51,52] Therefore, the present study only included patients who administered lorcaserin for ≥6 months and completed this period of administration before the withdrawal of lorcaserin.

Orlistat contributes to weight loss by inhibiting gastric and pancreatic lipases in the gastrointestinal tract, thereby reducing the absorption of dietary fat.[53] In a study conducted in Finland in which a low-calorie balanced diet and orlistat were used, reductions in body weight and fat mass, but not in fat-free mass or resting energy expenditure, occurred in the orlistat-treated group vs the placebo group.[54] In another randomized study of the administration of orlistat as an adjunct to lifestyle changes, orlistat caused significantly greater weight loss than placebo over 1 year (10.6 vs 6.2 kg).[55] Although orlistat caused weight loss in the present study, no significantly different changes in body composition occurred. The small number of participants in each of the AOM groups, and especially in the orlistat group, might explain the lack of

statistically significant differences among the groups in the present study. Orlistat is a safe medication for weight management, and can be used in patients with multiple comorbidities effectively and safely.[55]

The BMR is the daily rate of energy metabolism an individual needs to maintain essential physiologic functions, accounts for approximately 70% of total daily energy expenditure in humans, and it is principally determined by body composition, and especially FFM.[56] The loss of FFM that occurs alongside weight loss leads to a reduction in BMR that is often larger than would be expected in association with the changes that occur in body composition, a phenomenon that is referred to as metabolic adaptation.[57,58] An experimental study revealed that the maintenance of body weight at a level ≥10% below the initial level is associated with negative observed-minus-predicted values of energy expenditure, especially in individuals with obesity who achieve substantial weight loss.[57] This metabolic adaptation was also demonstrated by the results of "The Biggest Loser" competition, which showed that a lower metabolic rate can persist for >6 years, even though the body weight of most of the participants had returned to their initial values.[58] Therefore, changes in FFM and metabolic rate should be considered during the management of obesity, alongside weight loss and maintenance. There have been several previous studies of the changes in body composition that occur in users of AOMs. Liraglutide at a dose of 3 mg/day was found to reduce body fat by 15.4% in the absence of any significant loss of lean tissue (only −2.0%);[34] naltrexone/bupropion (at dosages of 16, 32, or 48 mg/day naltrexone in combination with 400 mg/day bupropion) caused substantial reductions in body fat (−14.0%) and visceral fat (−15%), while preserving lean mass (−3.0%);[59] and phentermine/topiramate at doses of 15/92 mg/day caused considerable reductions in body weight (−12.2 kg) and fat mass (−8.1 kg), with a minimal loss of lean mass (−3.3 kg).[60] In the present study, we compared the changes in body composition and BMR among the AOM groups. Consistent with the findings of previous studies, the body weight, BMI, and BFM of the participants had decreased significantly after 6 months of AOM administration (by −2.44 to −7.89 kg), but there were no significant changes in SMM (−1.03 to −2.56 kg). Notably, there were significant differences in the changes in BFM, which correlated with the changes in body weight, and the AOMs can be ranked as follows with respect to this outcome: phentermine, lorcaserin, phentermine/topiramate, liraglutide, orlistat, and naltrexone/bupropion. These findings suggest that lifestyle interventions in combination with AOMs are effective means of inducing a loss of body fat and maintaining BMR. To ensure the successful treatment of obesity, physicians should ensure that detailed dietary programs are prepared, such as a low-calorie diet involving a high protein intake of at least 1.2–1.5 g/kg/day; and that adequate physical activity is performed, including resistance exercise. These measures are essential to prevent the loss of fat-free mass (FFM) and a reduction in BMR during weight loss.

A number of limitations to the present study should be acknowledged. First, the 6-month study period was relatively short, which limits our ability to draw conclusions regarding the long-term effects of AOMs. The small number of patients who continued AOM therapy for more than 6 months, limited by financial considerations and low adherence, also impacts this evaluation. Second, the small number of participants in each AOM group made it difficult to obtain statistically significant differences between groups. Third, although obesity specialists provided an intensive lifestyle intervention program during visits, specific data regarding the daily total calorie intake, macronutrient ratios, and physical activity of each participant were not recorded. Fourth, there was no uniformity in the maximum doses of AOMs used or the amount of time taken to reach the maximum tolerable doses. Finally, our study did not encompass two drugs recently approved by the FDA for obesity management, Semaglutide and Tirzepatide, due to their unavailability in Korea during the study period and up to the present.[61,62] The significant efficacy of these drugs in promoting weight loss indicates that future research should include these novel AOMs.

Despite these limitations, the study also exhibits several notable strengths. First, this was the first study of its kind to directly compare the effects of the available AOMs in a real-world clinical setting in Korea, which adds significance to the findings of the study. Second, the mean BMI of the participants was approximately 35 kg/m^2, which represents morbid obesity, according to the Asia-Pacific obesity criteria. Because the risks of morbidity and mortality increase with the severity of obesity, the use of intensive treatment for individuals with morbid obesity is very important, and renders the present findings more valuable. Finally, we analyzed the changes in both body weight and body composition, which are practical methods of assessing the efficacy of obesity treatment. The monitoring of body composition in obesity clinics is essential to minimize the risk of metabolic adaptation and maintain long-term weight loss.

Conclusion

To conclude, in the present study, the efficacies of six AOMs (phentermine, phentermine/topiramate, liraglutide, naltrexone/bupropion, lorcaserin, and orlistat) were compared, and we found that all of these induced substantial weight loss, without significant changes in muscle mass, over a 6 month period. The short-term use of phentermine and the long-term use of phentermine/topiramate or liraglutide were found to be practical adjunct therapies for obesity. Nevertheless, it is necessary to conduct large-scale, long-term prospective studies to comprehensively characterize the efficacies of the various AOMs with respect to weight loss and maintenance. These studies should further strengthen our understanding and help refine the management of obesity.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Haslam DW, James WP. Obesity. *Lancet*. 2005;9492:1197–1209.
2. Report of a WHO consultation. Obesity: preventing and managing the global epidemic; 2000.
3. World Health Organization. Fact sheets - Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed June 9, 2021.
4. Bassett J. International diabetes I, world health organization regional office for the Western P, international association for the study of O, international obesity T. *Asia Pacific Persp*. 2000;2000:1.
5. Nam GE, Kim Y-H, Han K, et al. Obesity fact sheet in Korea, 2020: prevalence of obesity by obesity class from 2009 to 2018. *J Obes Metab Synd*. 2021;30(2):141–148. doi:10.7570/jomes21056
6. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American college of cardiology/American heart association task force on practice guidelines and the obesity society. *Circulation*. 2014;129 (25_suppl_2):S102–38. doi:10.1161/01.cir.0000437739.71477.ee
7. Goldstein DJ. Beneficial health effects of modest weight loss. *Internat J Obes Rel Metab Dis*. 1992;16(6):397–415.
8. Seo MH, Lee WY, Kim SS, et al. Korean society for the study of obesity guideline for the management of obesity in Korea. *J Obes Metab Synd*. 2018;28(1):40.
9. Wing RR, Hill JO. Successful W Eight Lossm Aintenance. *Ann Rev Nutrit*. 2001;21:323–341. doi:10.1146/annurev.nutr.21.1.323
10. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Associ*. 2007;107(10):1755–1767.
11. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. *Internat J Obes*. 2015;39:1188–1196. doi:10.1038/ijo.2015.59
12. Gomez-Arbelaez D, Crujeiras AA-O, Castro AI, et al. Resting metabolic rate of obese patients under very low calorie ketogenic diet. *Nutrit Metabol*. 2018;15. doi:10.1186/s12986-018-0249-z
13. Bauer J, Biolo G, Cederholm T, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group. *J Am Med Directors Assoc*. 2013;14(8):542–559. doi:10.1016/j.jamda.2013.05.021
14. The Korean Nutrition Society. Dietary reference intakes for Koreans 2020; 2020.
15. The Korean Nutrition Society. Recommended dietary allowances for Koreans, 7th revision Seoul; 2000.
16. Kim JAO. Optimal diet strategies for weight loss and weight loss maintenance. *J Obesit MetabSynd*. 2021;30:20–31. doi:10.7570/jomes20065
17. Jung J-G, Kim J-S, Yoon S-J, Lee S, Ahn S-K. Korean alcohol guidelines for primary care physician. *KJFP*. 2021;11(1):14–21. doi:10.21215/kjfp.2021.11.1.14
18. Kim B-Y, Kang SM, Kang J-H, et al. 2020 Korean society for the study of obesity guidelines for the management of obesity in Korea. *JOMES*. 2021;30(2):81–92. doi:10.7570/jomes21022
19. Smith KB, Smith MS. Obesity Statistics. *Primary Care*. 2016;43:121–135. doi:10.1016/j.pop.2015.10.001
20. Canuto RA-O, Garcez AA-O, de Souza RA-O, Kac GA-O, Olinto MA-O. Nutritional intervention strategies for the management of overweight and obesity in primary health care: a systematic review with meta-analysis. *Obes Rev*. 2021;22. doi:10.1111/obr.13143
21. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am*. 2018;102:183–197. doi:10.1016/j.mcna.2017.08.012
22. Tak YA-O, Lee SY. Long-term efficacy and safety of anti-obesity treatment: where do we stand? *Curr Obes Rep*. 2021;10:14–30. doi:10.1007/s13679-020-00422-w
23. Blonde LA-O, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Advan Therap*. 2018;35:1763–1774. doi:10.1007/s12325-018-0805-y
24. Administration FaD. Guidance for industry on developing products for weight management, 2007 February 15, 2007;National Archives and Records Administration; 2007:7441–7442.
25. Ko HJ, Kim JW, Lim SA-O. Adherence to and dropout from liraglutide 3.0 mg obesity treatment in a real-world setting. *J Obesit Metab Synd*. 2022;31:254–262. doi:10.7570/jomes22029
26. Melin I, Reynisdottir S, Fau - Berglund L, et al. Conservative treatment of obesity in an academic obesity unit. Long-term outcome and drop-out. *Eat Weig Disord*. 2006;11: 22–30. doi:10.1007/BF03327740
27. Inelmen EM, Toffanello ED, Enzi G, et al. Predictors of drop-out in overweight and obese outpatients. *Internat J Obes*. 2005;29(1):122–128.
28. Sulzer D, Sonders MS, Poulsen NW, Galli A. Mechanisms of neurotransmitter release by amphetamines: a review. *Prog Neurobiol*. 2005;75:406–433. doi:10.1016/j.pneurobio.2005.04.003
29. Narayanaswami V, Dwoskin LP. Obesity: current and potential pharmacotherapeutics and targets. *Pharmacol Therapeut*. 2017;170:116–147.

30. Hendricks EJ, Greenway FL, Greenway FL. How physician obesity specialists use drugs to treat obesity. *Obesity*. 2009;17:1730–1735. doi:10.1038/oby.2009.69

31. Hampp C, Borders-Hemphill V, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. *Pharmacotherapy*. 2013;33:1299–1307. doi:10.1002/phar.1342

32. Márquez-Cruz M, Kammar-García A, Huerta-Cruz JC, et al. Three- and six-month efficacy and safety of phentermine in a Mexican obese population. *Internat J Clin Pharmacol Therap*. 2021;59(8):539.

33. Hendricks EJ, Gupta AK, Westman EC, Gupta AK. Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity. *Obesity*. 2011;19:2351–2360. doi:10.1038/oby.2011.94

34. Astrup A, Carraro R, Fau - Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Internat J Obes*. 2012;36(6):843–854.

35. Ministry of Food and Drug Safety. Principles for safe use of psychotropic appetite suppressant. Narcotics Management Division. Available from: https://www.mfds.go.kr/brd/m_99/view.do?seq=44506. Accessed August 11, 2020.

36. Ioannides-Demos LL, McNeil JJ, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. *Drug Saf*. 2006;29:277–302. doi:10.2165/00002018-200629040-00001

37. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315:2424. doi:10.1001/jama.2016.7602

38. van Pelt RE, Dinneno FA, Seals DR, Jones PP. Age-related decline in RMR in physically active men: relation to exercise volume and energy intake. *Am J Physiol*. 2001;281(3):E633–E639.

39. D'Onofrio G, Kirschner J, Prather H, Goldman D, Rozanski A. Musculoskeletal exercise: its role in promoting health and longevity. *Prog Cardiovasc Dis*. 2023;77:25–36. doi:10.1016/j.pcad.2023.02.006

40. Lee M, Lauren BA-O, Zhan T, et al. The cost-effectiveness of pharmacotherapy and lifestyle intervention in the treatment of obesity. *Obes Sci Pract*. 2020;6:162–170. doi:10.1002/osp4.390

41. Sanyal D, Majumdar A. Low dose liraglutide in Indian patients with type 2 diabetes in the real world setting. *Ind J Endocrinol Metabol*. 2013;17:301. doi:10.4103/2230-8210.119629

42. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Internat J Obes*. 2014;38(6):784–793.

43. Farr OM, Tsoukas MA, Triantafyllou G, et al. Short-term administration of the GLP-1 analog liraglutide decreases circulating leptin and increases GIP levels and these changes are associated with alterations in CNS responses to food cues: a randomized, placebo-controlled, crossover study. *Metabolism*. 2016;65(7):945–953.

44. 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. doi:10.1056/NEJMoa1411892

45. Gorgojo-Martínez JA-O, Basagoiti-Carreño B, Sanz-Velasco A, Serrano-Moreno C, Almodóvar-Ruiz F. Effectiveness and tolerability of orlistat and liraglutide in patients with obesity in a real-world setting: the XENSOR Study. *Internat J Clin Pract*. 2019;73. doi:10.1111/ijcp.13399

46. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. *Obes Sci Pract*. 2017;3:3–14. doi:10.1002/osp4.84

47. Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374:1606–1616. doi:10.1016/S0140-6736(09)61375-1

48. Park JA, Kim JA-O, Choi JH, et al. Effectiveness of liraglutide 3 mg for the treatment of obesity in a real-world setting without intensive lifestyle intervention. *Intern J Obes*. 2021;45:776–786. doi:10.1038/s41366-021-00739-z

49. Trenson L, Trenson S, van Nes F, et al. Liraglutide for weight management in the real world: significant weight loss even if the maximal daily dose is not achieved. *Obesity Facts*. 2022;15(1):83–89.

50. Kim KK. Understanding the mechanism of action and clinical implications of anti-obesity drugs recently approved in Korea. *Korean J Fam Med*. 2019;40:63–71. doi:10.4082/kjfm.19.0013

51. Sharretts J, Galescu O, Gomatam S, Andraca-Carrera E, Hampp C, Yanoff L. Cancer risk associated with lorcaserin - The FDA's review of the CAMELLIA-TIMI 61 trial. *New Engl J Med*. 2020;383:1000–1002. doi:10.1056/NEJMp2003873

52. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. *New England Journal of Medicine*. 2018;379:1107–1117. doi:10.1056/NEJMoa1808721

53. Heck AM, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacotherapy*. 2000;20(3):270–279.

54. Karhunen L, Franssila-Kallunki A, Rissanen P, et al. Effects of Orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. *Intern J Obes Relat Metab Dis*. 2001;24:1567–1572. doi:10.1038/sj.ijo.0801443

55. Torgerson JS, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Clin Diabetol*. 2004;5(2):95–104.

56. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. *Publ Health Nutrit*. 2005;8:1133–1152. doi:10.1079/PHN2005801

57. Leibel RL, Rosenbaum M, Fau - Hirsch J, Hirsch J. Changes in energy expenditure resulting from altered body weight. *New Engl J Med*. 1995;332:621–628. doi:10.1056/NEJM199503093321001

58. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. *Obesity*. 2016;24:1612–1619. doi:10.1002/oby.21538

59. Smith SR, Fujioka K, Gupta AK, et al. Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. *Diab Obesit Metab*. 2013;15(9):863–866. doi:10.1111/dom.12095

60. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, Phase 3 trial. *Lancet*. 2011;377 (9774):1341–1352. doi:10.1016/S0140-6736(11)60205-5

61. 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. doi:10.1056/NEJMoa2032183

62. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205–216. doi:10.1056/NEJMoa2206038