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A Review of Lifestyle Interventions Provided as an Adjunct to Obesity Management Medications

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ABSTRACT

Objective: This review synthesized the components of lifestyle interventions that have been provided in Phase 3 trials of obesity management medications (OMMs).

Methods: PubMed, CINAHL, and EMBASE were searched for Phase 3 clinical trials published from inception to February 2026 that tested FDA-approved OMMs. We descriptively synthesized lifestyle intervention components including dietary, physical activity, and delivery of counseling.

Results: We included 50 reports from 42 studies. Most of the studies included a calorie restriction goal of 500 kcals/day. The most common physical activity goal recommended was $\geq$ 150 min/week. Diaries for eating and tracking physical activity have been recommended in many studies. There were 22 studies that provided counseling at least monthly or more frequently and an additional 16 trials that provided counseling at least every 3 months.

Conclusions: Lifestyle interventions have been core components in Phase 3 trials of FDA-approved OMMs. Further research is needed to test the optimal lifestyle interventions that should be provided along OMMs to maximize health outcomes.

1 | Introduction

Lifestyle intervention has long been considered the foundation of obesity treatment [1]. Such treatment includes behavioral strategies that help individuals improve their nutrition and increase physical activity, with the overall goal of creating a caloric deficit to produce weight loss. Intensive lifestyle interventions, typically defined as visits that focus on diet, physical activity, and behavioral changes and occur at least 14 sessions in the first six months of treatment with monthly counseling for maintenance [2], have produced clinically significant losses of $\geq$ 5% of initial weight with associated improvements in health outcomes [3, 4]. However, there have been persistent limitations with lifestyle treatment, including difficulties with achieving and sustaining larger weight losses and challenges with dissemination and implementation in clinical practice [5, 6].

To help bolster the weight loss and improve long-term weight loss, several trials have tested first-generation obesity management medications (OMMs; i.e., orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide). First-generation OMMs tend to produce average initial weight losses of $<$ 10% but can range from mean losses of 6.1% with naltrexone/bupropion to 10.9% with phentermine/topiramate [7]. Importantly, combining first-generation OMMs with intensive lifestyle treatment appears to have additive weight loss effects. One of the first demonstrations of the role of intensive lifestyle treatment in enhancing weight loss with first-generation OMMs was by Wadden and

colleagues in a 1-year randomized controlled trial that examined sibutramine alone, sibutramine plus lifestyle (weekly group lifestyle modification for 20 weeks then monthly), or sibutramine plus lifestyle and a 16-week portion-controlled diet [8]. Participants in sibutramine alone lost 4.1% of initial body weight, which was significantly less than the drug plus lifestyle group who lost 10.8% and the sibutramine plus lifestyle and portion-controlled diet group who lost 16.5% of initial weight [8]. These studies demonstrated that first-generation OMMs, when combined with more intensive lifestyle intervention, helped to add additional weight loss to the modest weight loss efficacy seen with first-generation OMMs compared with less intensive interventions [1, 8, 9]. However, with the high efficacy and increasing uptake of the second-generation OMMs (i.e., semaglutide and tirzepatide), some have questioned the importance and role of lifestyle intervention [10].

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), which mimics the action of the endogenously occurring hormone GLP-1 to regulate appetite and decrease caloric intake [11, 12]. It also reduces blood glucose by promoting insulin secretion and decreasing glucagon secretion in a glucose-dependent manner [12]. Tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA that simulates the effects of GLP-1 as well as the incretin hormone GIP [13]. GIP contributes to lowering postprandial glucose and influencing appetite and food intake [14, 15]. Both medications were first approved as subcutaneous, once weekly injections. An oral version of semaglutide was approved by the FDA for obesity treatment in December 2025. Incretin-based medications were originally developed for the treatment of type 2 diabetes mellitus. The first incretin-based medication, exenatide, was approved by the US Food and Drug Administration (FDA) for type 2 diabetes in 2005. Liraglutide was the first incretin-based medication that was FDA approved for obesity treatment in 2014 as a once-daily subcutaneous injectable. Liraglutide 3.0 mg daily resulted in losses of 8.0% of initial weight, compared to losses of 2.6% with placebo, at 56 weeks [16] In pivotal Phase 3 trials, semaglutide 2.4 mg weekly (injectable) and tirzepatide 15 mg weekly resulted in losses of 14.9% [17] and 20.9% [18] of initial weight at 68 and 72 weeks, respectively. High dose injectable semaglutide 7.2 mg weekly was approved by the FDA in 2026 and in Phase 3 trials resulted in 18.7% initial weight loss at 72 weeks [19] Oral semaglutide 25 mg daily resulted in losses of 13.6% of initial weight at 64 weeks [20].

While there is much excitement surrounding these medications, it is often underappreciated that all OMMs are tested and prescribed as an adjunct to a reduced-calorie diet and increased physical activity as mandated by regulatory bodies such as the U.S. Food and Drug Administration (FDA). Regulatory oversight of weight-reduction medications has strengthened over time, particularly through guidance issued by the U.S. Food and Drug Administration (FDA). The FDA released formal guidance for the development of weight-loss products in 1996 [21], 2007, and most recently in 2025. The 2007 guidance for Phase 3 clinical trials recommended that weight-reduction medications be evaluated alongside a lifestyle-modification program similar to what patients would follow after approval [22]. This program was intended to balance effectiveness with practicality for real-world use. The guidance was updated in 2025 and continues to emphasize that Phase 3 trials should test weight-loss drugs as an add-on to recommendations for diet and physical activity [23]. Specifically, trials should include a standard-of-care diet and physical-activity program that is both effective and simple enough to be implemented in primary care settings. There has not been a previous review that has synthesized the components of lifestyle interventions that have been provided in Phase 3 trials with OMMs. Such information is critical to the field due to the potential for the lifestyle intervention to have added additional weight loss and bolstered adherence to the medication. In addition, to date, there is no consensus regarding the best lifestyle intervention to use with highly efficacious OMMs. It is important to understand what has been tested in conjunction with OMMs to better understand ways that lifestyle intervention may be translated to clinical practice and potentially improved to promote optimal health outcomes. The purpose of this narrative review was to synthesize the lifestyle modification program components that have been provided as an adjunct to FDA-approved OMMs in Phase 3 trials of adults with overweight or obesity. Our objectives were to comprehensively describe the dietary, physical activity, and behavioral strategies used in such trials.

2 | Materials & Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) algorithm to guide this review [24]. The literature search was conducted in PubMed, CINAHL, and EMBASE without language restrictions for clinical trials and randomized controlled trials published from inception to March 2025. The search was updated during the peer review process to February 2026. For our primary search, we used the following search terms: “obes*” or “overweight” or “weight” AND “anti-obesity” or “pharmacotherapy” or “medication” or “orlistat” or “tirzepatide” or “semaglutide” or “liraglutide” or “naltrexone” or bupropion” or “phentermine” or “topiramate.” We performed a hand search by reviewing reference lists of the included studies. The search was restricted to studies evaluating the use of FDA-approved medications for obesity treatment in Phase 3 studies (i.e., orlistat, phentermine/topiramate, liraglutide, bupropion/naltrexone, oral and injectable semaglutide, and tirzepatide). We conducted a search using similar terms on ClinicalTrials.gov.

2.1 | Eligibility Criteria

Our inclusion criteria were articles: published in English, enrolled adult participants (aged 18 years and above), included patients with overweight or obesity (e.g., BMI $\geq$ 25 kg/m^2, or BMI $\geq$ 23 kg/m^2 for Asian populations), used a randomized, placebo-controlled design with an FDA-approved medication for chronic weight management, conducted as a Phase 3 study, and reported primary trial results and/or protocol description. Because the field of obesity pharmacotherapy is changing quickly, we also included trials of recently FDA-approved medications even when they tested doses that are not themselves FDA-approved for obesity. For example, we included the OASIS 1 trial [25], which tested oral semaglutide 50 mg daily, even though the 25 mg daily dose evaluated in the OASIS 4 trial

[20] is the dose approved for obesity treatment in the US. Articles that included descriptions of protocols of the included studies were also reviewed. We excluded observational studies, case-studies, reviews, meta-analyses, abstracts, and secondary/post-hoc analyses. We also excluded studies that included participants with monogenetic forms of obesity.

2.2 | Study Selection

Screening of the title and abstracts was performed, and then the full text of potentially eligible studies was assessed. Search, selection, and analysis of the selected studies were performed independently by two reviewers; disagreements were resolved by consensus with the primary raters and a senior investigator.

2.3 | Data Extraction and Analysis

For all included studies, we reviewed the study articles and supplementary materials including study protocols where available to extract data. A predefined Excel spreadsheet was used for data extraction. Data included study characteristics (e.g., year of study, duration of study, medication, weight loss for placebo and medication groups), and lifestyle intervention components including dietary, physical activity, and delivery of counseling (frequency, mode, and provider).

3 | Results

The characteristics of the included studies are summarized in Table 1. We included 50 reports from 42 studies. The articles were on orlistat (2 articles on 1 trial) [26, 27]; phentermine/topiramate (3 reports on 2 studies including 1 with an extension) [28–30]; liraglutide (6 articles on 5 trials including 1 with an extension) [16, 31–35]; naltrexone/bupropion (4 studies) [9, 36–38]; injectable semaglutide (18 reports on 16 studies) [17, 19, 39–54]; tirzepatide (14 articles reporting on 11 studies including 1 with an extension) [18, 55–67]; and oral semaglutide (3 reports on 3 studies) [20, 25, 68]. Of the included studies, 34 had a minimum age of 18 years, 2 included adults $\geq$ 18 years in certain included countries and $\geq$ 20 years in Japan, 1 included adults $\geq$ 18 in Thailand and $\geq$ 19 in South Korea, and the 5 others had older minimum age cut-offs. There were 34 studies that had no maximum age and the remaining studies had maximum age ranges between 60 and 70 years. BMI was used to define obesity in all studies. The most common study criteria were that all participants had to have either a BMI $\geq$ 27 kg/m^2 with an obesity-related comorbidity and/or a BMI $\geq$ 30 kg/m^2 (n = 31). In total, 30 studies excluded participants with type 2 diabetes, 6 studies included only participants with type 2 diabetes, and 6 included both participants with and without type 2 diabetes. Other major co-occurring conditions included prediabetes (n = 3; including 2 reports that were extensions of primary studies that included people with and without prediabetes); obstructive sleep apnea (n = 2); heart failure with preserved ejection fraction (n = 2); knee osteoarthritis (n = 1); established cardiovascular disease (n = 1); and established cardiovascular disease or multiple cardiovascular risk factors (n = 1).

There were 2 trials that included an intensive lifestyle intervention prior to being randomized to a medication (SCALE Maintenance and SURMOUNT 3) and 3 trials that had a medication lead-in and then participants were randomized to continue the medication or switch to placebo (STEP 4 and SURMOUNT 4) or to continue the medication or switch to a lower dose or to placebo (SURMOUNT-Maintain). Excluding studies that had a run-in of either intensive lifestyle intervention or medication, the average change in weight for each study in the placebo arm ranged from −0.9% to −5.1% of initial body weight.

3.1 | Dietary Component

Dietary recommendations were included in 40 studies, though details were variable (Table 2). Most of the studies included a restriction of 500 kcals/day for the entirety of the study (n = 28) or for at least 1 phase of the study (n = 2). One study had a restriction of 800 kcals/day (n = 1). The caloric deficits were computed from the equations for total energy expenditure. Other studies used set calorie targets based on baseline body weight or sex, such as 1200 kcals per day for a participant $\leq$ 249 lbs (n = 4). Five studies included general guidance for a reduced-calorie diet or individualized healthy eating plan but did not specify the target caloric amount. Several studies included that the prescription would be recalculated without a caloric deficit if a participant's BMI was $\leq$ 20 kg/m^2 (n = 1), $\leq$ 22 kg/m^2 (n = 10), or $\leq$ 22.5 kg/m^2 (n = 11). Macronutrient targets were specified in 15 trials. The majority included a protein goal of 20% (n = 11) or 15%–20% (n = 4). Micronutrients (vitamins A, D, E, and K) were tested in 1 study [26, 27]. Food diaries were recommended daily in 13 studies. A 3-day food diary was recommended about every 2 months in 3 studies or prior to each counseling visit in 8 trials. Meal replacements were used in 2 studies for the lead in (prior to starting an OMM) and 1 study used the meal replacements concurrently while taking a medication.

3.2 | Physical Activity

The most common physical activity goal recommended was $\geq$ 150 min/week (n = 25; Table 3). Other studies used initial physical activity targets of $\geq$ 100 min/week (n = 2) or 180 min per week (n = 1) and then had the targets gradually increase for weight loss maintenance (ranges recommended in each of the studies were $\geq$ 200, $\geq$ 250, and 360 min/week; n = 3). Aerobic activity (e.g., brisk walking) was suggested in 23 trials. Resistance exercise was suggested in 1 study. Six studies provided participants with a pedometer/activity tracker. Activity tracking was recommended daily (n = 12) or 3 day prior to each counseling visit (n = 8).

3.3 | Behavioral Component

There were 22 studies that provided counseling at least monthly or more frequently and an additional 16 trials that provided counseling at least every 3 months (Table 4). Some studies kept the same cadence of visits throughout the entire study with approximately monthly visits (n = 15; Table 4) or every 3 months (n = 2). However, most studies went from a higher, more intensive to a lower frequency of counseling visits (n = 22). The higher frequencies were typically during dose escalation of the medication or an intensive lifestyle lead-in phase prior to the medication (Table 4). In most studies

TABLE 1 | Study characteristics and weight losses.

			Participant characteristics								Weight loss (intention-to-treat)	
			Age (yrs)	BMI			Type 2 diabetes	Other major condition				
Trial name	Study phase	Purpose of study		≥ 27 kg/m² + obesity-related comorbidity	≥ 30 kg/m²	Other threshold			Medication	Time (Wk)	Placebo	Medication
XENDOS [26, 27]	Main	Orlistat 120 mg TID versus placebo	30–60		X		Excluded		Orlistat 120 mg TID	Baseline to 52	6.2 kg	10.6 kg
										Baseline to 208	3.0 kg	5.8 kg
EQUIP [28]	Main	PHEN/TPM 3.75/23 daily or PHEN/TPM 15/92 daily versus placebo	18–70			BMI ≥ 35	Fasting serum glucose level ≤ 110 mg/dL	Triglycerides ≤ 200 mg/dL with treatment of 0–1 lipid-lowering medication, BP ≤ 140/90 mm Hg with treatment of 0–2 antihypertensive medications, and fasting serum glucose level ≤ 110 mg/dL	PHEN/TPMCR 3.75/23 mg daily	Baseline to 56	1.6%	5.1%
									PHEN/TPM CR 15/92 mg daily	Baseline to 56		10.9%
CONQUER [29]	Main	PHEN/TPM 7.5/46 daily or PHEN/TPM 15/92 daily versus placebo	18–70			BMI 27–45 (no lower BMI for those with baseline diabetes)	Included (15.8% of sample)	≥ 2 pre-specified comorbidities at baseline	PHEN/TPM CR 7.5/46 mg daily	Baseline to 56	1.2%	7.8%
									PHEN/TPM CR 15/92 mg daily			9.8%
SEQUEL [30]	Extension of CONQUER (52 weeks)	PHEN/TPM 7.5/46 daily or PHEN/TPM 15/92 daily versus placebo	See CONQUER trial			> 22 at completion of CONQUER study	Included (21.5% of sample)	Completed CONQUER study on treatment; complied with protocol requirements	PHEN/TPM CR 7.5/46 daily	Baseline to 108	1.8%	9.3%
									PHEN/TPM CR 15/92 daily			10.5%
SCALE obesity and prediabetes [16, 31]	Main	Liraglutide 3.0 mg daily versus placebo	≥ 18	X (treated or untreated dyslipidemia and/or hypertension)	X		Excluded		Liraglutide 3.0 mg daily	Baseline to 56	2.6%	8.0%
	Extension (104 weeks)	Liraglutide 3.0 mg daily versus placebo						Main trial criteria + prediabetes at screening	Liraglutide 3.0 mg daily	Baseline to 160	1.9%	6.1%
SCALE diabetes [32]	Main	Liraglutide 1.8 mg daily or liraglutide 3.0 mg daily versus placebo	≥ 18	X			Included (100%)		Liraglutide 1.8 mg daily	Baseline to 56	2.0%	4.7%
									Liraglutide 3.0 mg daily			6.0%

(Continues)

TABLE 1 | (Continued)

			Participant characteristics								Weight loss (intention-to-treat)	
			Age (yrs)	BMI			Type 2 diabetes	Other major condition				
Trial name	Study phase	Purpose of study		≥ 27 kg/m² + obesity-related comorbidity	≥ 30 kg/m²	Other threshold			Medication	Time (Wk)	Placebo	Medication
SCALE sleep apnea [33]	Main	Liraglutide 3.0 mg daily versus placebo	18–64		X		Excluded	Moderate or severe obstructive sleep apnea; unable or unwilling to use CPAP	Liraglutide 3.0 mg daily	Baseline to 32	1.6%	5.7%
SCALE IBT [34]	Main	Liraglutide 3.0 mg daily + IBT versus placebo + IBT	≥ 18		X		Excluded		Liraglutide 3.0 mg daily	Baseline to 56	4.0%	7.5%
SCALE maintenance [35]	Main: LCD run-in	LCD run-in then randomized to liraglutide 3.0 mg daily versus placebo for maintenance	≥ 18	X (treated or untreated dyslipidemia and/or hypertension)	X		Excluded		N/A	Variable, 4–12	6.0%	5.9%
	Main: RCT of liraglutide versus placebo							Lost ≥ 5% of initial body weight during LCD run-in	Liraglutide 3.0 mg daily	Randomization to 56	0.2% (from randomization)	6.2% (from randomization)
COR-I [36]	Main	Naltrexone SR (16 mg)/bupropion SR (360 mg) daily or naltrexone SR (32 mg)/bupropion SR (360 mg) daily versus placebo	18–65			BMI 30–45 or BMI 27–45 + dyslipidemia and/or hypertension	Excluded		Naltrexone SR (16 mg)/bupropion SR (360 mg) daily	Baseline to 56	1.3%	5.0%
									Naltrexone SR (32 mg)/bupropion SR (360 mg) daily			6.1%
COR-II [37]	Main	Naltrexone SR (32 mg)/bupropion SR (360 mg) daily versus placebo	18–65			BMI 30–45 or BMI 27–45 + dyslipidemia and/or hypertension	Excluded		Naltrexone SR (32 mg)/bupropion SR (360 mg) versus placebo	Baseline to 56	1.2%	6.4%
COR-diabetes [38]	Main	Naltrexone SR (32 mg)/bupropion SR (360 mg) daily versus placebo	18–70			≥ 27 and ≤ 45	Included (100%)		Naltrexone SR (32 mg) SR/bupropion (360 mg)	Baseline to 56	1.8%	5.0%
COR-BMOD [9]	Main	Placebo + BMOD versus naltrexone SR (32 mg)/bupropion SR (360 mg) daily + BMOD	18–65			BMI 30–45 or BMI 27–45 + dyslipidemia and/or hypertension	Excluded		Naltrexone SR (32 mg) SR/bupropion (360 mg) SR in two divided doses	Baseline to 56	5.1%	9.3%

(Continues)

TABLE 1 | (Continued)

Trial name	Study phase	Purpose of study	Participant characteristics: Age (yrs)	BMI: ≥ 27 kg/m² + obesity-related comorbidity	BMI: ≥ 30 kg/m²	BMI: Other threshold	Type 2 diabetes	Other major condition	Medication	Time (Wk)	Weight loss (intention-to-treat): Placebo	Weight loss (intention-to-treat): Medication
STEP 1 [17, 39]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18	X	X		Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 68	2.4%	14.9%
STEP 2 [39, 40]	Main	Semaglutide 2.4 mg weekly or semaglutide 1.0 mg weekly versus placebo	≥ 18	X			Included (100%)		Semaglutide 1.0 mg weekly (injectable)	Baseline to 68	3.4%	7.0%
									Semaglutide 2.4 mg weekly (injectable)			9.6%
STEP 3 [39, 41]	Main: Phase I (IBT with LCD + semaglutide versus IBT with LCD + placebo	IBT + semaglutide versus IBT + placebo	≥ 18	X	X		Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 8	N/A	NR
	Main: Phase II (IBT + semaglutide vs. IBT + placebo)								Semaglutide 2.4 mg weekly (injectable)	Baseline to 68	5.7%	16.0%
STEP 4 [39, 42]	Main: Semaglutide lead-in	Semaglutide run-in then randomized to semaglutide 2.4 mg weekly versus placebo for maintenance	≥ 18	X	X		Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 20	10.6%	10.6%
	Main: Semaglutide versus placebo							Attained target maintenance dose of 2.4 mg weekly by week 16 and continued taking until week 20	Semaglutide 2.4 mg weekly (injectable)	20 to 68	Gain 6.9%	7.9% (additional loss)
STEP 5 [39, 43]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18	X	X		Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 104	2.6%	15.2%
STEP 6 [44]	Main	Semaglutide 1.7 mg weekly or semaglutide 2.4 mg weekly versus placebo	≥ 18 in South Korea; ≥ 20 in Japan			≥ 27 + ≥ 2 weight-related comorbidities or ≥ 35 + ≥ 1 weight-related comorbidity[a]	Included (25%)		Semaglutide 1.7 mg weekly (injectable)	Baseline to 68	2.1%	9.6%
									Semaglutide 2.4 mg weekly (injectable)			13.2%
STEP 7 [45]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18	X	X		Included (26%)		Semaglutide 2.4 mg weekly (injectable)	Baseline to 44	3.6%	12.1%

(Continues)

TABLE 1 | (Continued)

Trial name	Study phase	Purpose of study	Participant characteristics						Weight loss (intention-to-treat)			
			Age (yrs)	BMI			Type 2 diabetes	Other major condition				
				≥ 27 kg/m² + obesity-related comorbidity	≥ 30 kg/m²	Other threshold			Medication	Time (Wk)	Placebo	Medication
STEP 8 [46]	Main	Semaglutide 2.4 mg weekly versus liraglutide 3.0 mg daily	≥ 18	X	X		Excluded		Liraglutide 3.0 mg daily	Baseline to 68	1.9%	6.4%
									Semaglutide 2.4 mg weekly (injectable)			15.8%
STEP 9 [47]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Excluded	Knee osteoarthritis	Semaglutide 2.4 mg weekly (injectable)	Baseline to 68	3.2%	13.7%
STEP 10 [48]	Main (52 weeks)	Semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Excluded	Prediabetes at baseline	Semaglutide 2.4 mg weekly (injectable)	Baseline to 52	2.7%	13.9%
STEP 11 [49]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18 in Thailand and ≥ 19 in South Korea			≥ 25	Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 44	3.1%	16.0%
STEP HFpEF [50]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Excluded	HFpEF	Semaglutide 2.4 mg weekly (injectable)	Baseline to 52	2.6%	13.3%
STEP HFpEF DM [51]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Included (100%)	HFpEF	Semaglutide 2.4 mg weekly (injectable)	Baseline to 52	3.4%	9.8%
STEP UP [19]	Main	Semaglutide 7.2 mg weekly versus semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Excluded		Semaglutide 2.4 mg weekly (injectable)	Baseline to 72	3.9%	15.6%
									Semaglutide 7.2 mg weekly (injectable)	Baseline to 72		18.7%
STEP UP T2D [52]	Main	Semaglutide 7.2 mg weekly versus semaglutide 2.4 mg weekly versus placebo	≥ 18		X		Included (100%)		Semaglutide 2.4 mg weekly (injectable)	Baseline to 72	3.9%	10.4%
									Semaglutide 7.2 mg weekly (injectable)	Baseline to 72		13.2%
SELECT [53, 54]	Main	Semaglutide 2.4 mg weekly versus placebo	≥ 45	X			Excluded	Established cardiovascular disease	Semaglutide 2.4 mg weekly (injectable)	Baseline to 104	0.9%	9.4%

(Continues)

TABLE 1 | (Continued)

Trial name	Study phase	Purpose of study	Participant characteristics: Age (yrs)	BMI: ≥ 27 kg/m² + obesity-related comorbidity	BMI: ≥ 30 kg/m²	BMI: Other threshold	Type 2 diabetes	Other major condition	Medication	Time (Wk)	Weight loss (intention-to-treat): Placebo	Weight loss (intention-to-treat): Medication
SURMOUNT 1 [18, 55, 56]	Main	Tirzepatide 5 mg weekly or tirzepatide 10 mg weekly or tirzepatide 15 mg weekly versus placebo	≥ 18	X	X		Excluded		Tirzepatide 5 mg weekly	Baseline to 72	3.1%	15.0%
									Tirzepatide 10 mg weekly			19.5%
									Tirzepatide 15 mg weekly			20.9%
	Extension							Prediabetes at baseline	Tirzepatide 5 mg weekly	Baseline to 176	1.3%	12.3%
									Tirzepatide 10 mg weekly			18.7%
									Tirzepatide 15 mg weekly			19.7%
SURMOUNT 2 [55, 57]	Main	Tirzepatide 10 mg weekly or tirzepatide 15 mg weekly versus placebo	≥ 18	X			Included (100%)		Tirzepatide 10 mg weekly	Baseline to 72	3.2%	12.8%
									Tirzepatide 15 mg weekly			14.7%
SURMOUNT 3 [55, 58]	Main: ILI run-in	ILI run-in then randomized to tirzepatide MTD versus placebo for maintenance	≥ 18	X	X		Excluded		N/A	Baseline to 12 (randomization)	6.9% (only included those randomized who achieved ≥ 5% initial weight loss)	6.9%
	Main: Tirzepatide MTD versus placebo							Achieved ≥ 5.0% weight reduction during ILI run-in	Tirzepatide MTD weekly (10 or 15 mg)	Randomization (week 0) to 72 (84 weeks including ILI lead-in)	Gain 2.5%	18.4%
SURMOUNT 4 [55, 59]	Main: Tirzepatide run-in	Tirzepatide MTD run-in then randomized to tirzepatide MTD weekly (10 or 15 mg) versus placebo for maintenance	≥ 18	X	X		Excluded		Tirzepatide MTD weekly (10 or 15 mg)	Baseline to 36 (randomization)	20.9% (only included participants randomized)	20.9%
	Main: Tirzepatide versus placebo								Tirzepatide MTD weekly (10 or 15 mg)	Randomization (week 36) to 88	Gain 14.0%	5.5%

(Continues)

TABLE 1 | (Continued)

			Participant characteristics							Weight loss (intention-to-treat)	
			Age (yrs)	BMI			Type 2 diabetes	Other major condition			
Trial name	Study phase	Purpose of study		≥ 27 kg/m² + obesity-related comorbidity	≥ 30 kg/m²	Other threshold			Medication	Time (Wk)	Placebo	Medication
SURMOUNT 5 [60]	Tirzepatide versus semaglutide versus placebo	Tirzepatide MTD weekly (10 or 15 mg) versus semaglutide MTD (1.7 or 2.4 mg)	≥ 18	X	X		Excluded		Tirzepatide MTD weekly (10 or 15 mg)	Baseline to 72		20.2%
									Semaglutide MTD weekly (1.7 or 2.4 mg, injectable)			13.7%
SURMOUNT OSA [61, 62]	Main: Trial 1	Tirzepatide MTD weekly (10 or 15 mg) versus placebo	≥ 18		X	≥ 27 in Japan	Excluded	Moderate-to-severe obstructive sleep apnea; not receiving PAP	Tirzepatide MTD weekly (10 or 15 mg)	Baseline to 52	1.6%	17.7%
	Main: Trial 2				X	≥ 27 in Japan	Excluded	Moderate-to-severe obstructive sleep apnea; receiving PAP	Tirzepatide MTD weekly (10 or 15 mg)		2.3%	19.6%
SURMOUNT CN [63]	Main	Tirzepatide 10 mg or tirzepatide 15 mg versus placebo	≥ 18			BMI ≥ 28 or ≥ 24 + ≥ 1 weight-related comorbidity	Excluded		Tirzepatide 10 mg weekly	Baseline to 52	2.3%	13.6%
									Tirzepatide 15 mg weekly	Baseline to 52		17.5%
SURMOUNT J [64]	Main	Tirzepatide 10 mg or tirzepatide 15 mg versus placebo	≥ 20			BMI ≥ 27 kg/m² and < 35 + ≥ 2 obesity-related health disorders or ≥ 35 kg/m² + ≥ 1 obesity-related health disorder	Excluded		Tirzepatide 10 mg weekly	Baseline to 72	1.7%	17.8%
SURMOUNT MMO [65]	Main	Tirzepatide MTD versus placebo	> 40	X			Excluded	Established cardiovascular disease or multiple cardiovascular risk factors	Tirzepatide MTD weekly (5, 10, 15 mg)	Baseline to ~264 years	NR	NR
SURMOUNT-maintain [66]	Main: Tirzepatide lead-in		≥ 18	X	X		Excluded			Baseline to 60	NR	NR
	Main: Tirzepatide 5 mg weekly and tirzepatide MTD (10 or 15 mg) versus placebo			X	X		Excluded	Tolerating tirzepatide 10 or 15 mg without a change in dose between week 48 and 60; achieved ≥ 5.0% weight reduction during lead-in		Randomization (week 60) to 52	NR	NR
SUMMIT [67]	Main	Tirzepatide MTD versus placebo	≥ 40		X		Included (48.2%)	HFpEF	Tirzepatide 15 mg weekly	Baseline to 52	2.2%	13.9%
OASIS 1 [25]	Main	Semaglutide 50 mg versus placebo	≥ 18; ≥ 20 in Japan	X	X		Excluded		Semaglutide 50 mg daily (oral)	Baseline to 68	2.4%	15.1%

(Continues)

TABLE 1 | (Continued)

Trial name	Study phase	Purpose of study	Participant characteristics								Weight loss (intention-to-treat)	
			Age (yrs)	BMI			Type 2 diabetes	Other major condition	Medication	Time (Wk)	Placebo	Medication
				≥ 27 kg/m² + obesity-related comorbidity	≥ 30 kg/m²	Other threshold						
OASIS 2 [68]	Main	Semaglutide 50 mg versus placebo	≥ 18			BMI of ≥ 27 with ≥ 2 weight-related complications BMI of ≥ 35 with ≥ 1 weight-related complications	Included (25%)		Semaglutide 50 mg daily (oral)	Baseline to 68	1.3%	14.3%
OASIS 4 [20]	Main	Semaglutide 25 mg versus placebo	≥ 18	X	X		Excluded		Semaglutide 25 mg daily (oral)	Baseline to week 64	2.2%	13.6%

Abbreviations: BMI = body mass index, BMOD = behavioral modification, COR = Contrave Obesity Research, CPAP = continuous positive airway pressure, DM = diabetes mellitus, HFpEF = heart failure with preserved ejection fraction, IBT = intensive behavioral therapy, LCD = low-calorie diet, MTD = maximum tolerated dose, NR = not reported, OASIS = Oral Semaglutide Treatment Effect in People with Obesity, OSA = obstructive sleep apnea, PHEN = phentermine, SCALE = Satiety and Clinical Adiposity- Liraglutide Evidence, SELECT = Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity, SR = sustained release, STEP = Semaglutide Treatment Effect in People with Obesity, TID = three times a day, TPM = topiramate, Wk = weeks, XENDOS = XENical in the prevention of diabetes in obese subjects.

[a]At least 1 comorbidity had to be hypertension or dyslipidemia, or in Japan only, type 2 diabetes.

counseling was by a dietician/similar qualified healthcare professional ($n = 29$). Only a few studies ($n = 6$) stated that they used a treatment manual, of which most were based on the LEARN Manual or Diabetes Prevention Program. Most studies used both in-person and remote counseling (Table 4).

3.4 | Intensive Lifestyle Interventions

There were 3 studies that included intensive lifestyle intervention concurrently with a medication (SCALE IBT; COR-BMOD; STEP 3) and 2 trials that included an intensive lifestyle intervention prior to being randomized to a medication (SCALE Maintenance, SURMOUNT 3). Across the three studies that included concurrent intensive lifestyle intervention with a medication, participants received structured lifestyle treatment combining dietary modification, physical activity goals, and behavioral counseling based on structured manuals, with contact frequency tapering over time. In SCALE-IBT, participants had 15-min individual intensive behavioral therapy sessions delivered by registered dietitians, occurring weekly during the first month, biweekly from months 2–6, and monthly thereafter. They were prescribed a 1200–1800 kcal/day diet based on baseline weight, consisting of conventional foods with a balanced macronutrient distribution (~15%–20% protein, 20%–35% fat, remainder carbohydrates), and were encouraged to gradually increase physical activity to 250 min per week. Similarly, COR-BMOD used comparable dietary recommendations but differed in delivery and intensity, providing 90-min group sessions led by dietitians, behavioral psychologists, or exercise specialists, held weekly for 16 weeks, biweekly for 12 weeks, and monthly thereafter, with a higher physical activity goal of 360 min per week. STEP 3 incorporated a more structured dietary approach, beginning with a 1000–1200 kcal/day plan using meal replacements and pre-prepared meals for the first 8 weeks before transitioning to a 1200–1800 kcal/day conventional food diet based on baseline weight. Participants were advised to achieve 200 min of physical activity per week and received IBT counseling from a dietitian or similarly qualified professional on a tapered schedule (weekly during weeks 0–12, biweekly during weeks 12–24, and monthly thereafter up to week 68), with longer initial sessions (30–45 min) followed by shorter sessions (20–30 min). Overall, while all three interventions emphasize calorie restriction, gradual increases in physical activity, and decreasing counseling frequency over time, they differ in session format, intensity, and use of structured dietary tools such as meal replacements.

Two trials incorporated an intensive lifestyle intervention before randomization to pharmacotherapy, both emphasizing early weight loss through calorie restriction, meal replacements, and behavioral support. In the SCALE Maintenance trial, participants completed a 4–12-week low-calorie run-in phase with a 1200–1400 kcal/day diet that included up to three liquid meal replacements, along with biweekly face-to-face visits with a nutritionist and alternating weekly telephone support, and a physical activity goal of 150 min per week. Once participants achieved at least 5% initial weight loss, they were randomized to medication versus placebo. Participants were then prescribed a calorie-reduced (500 kcal/day deficit) balanced diet and continued counseling through brief (15–20 min) face-to-face sessions held weekly for the first month and monthly

TABLE 2 | Dietary components of phase 3 trials of obesity management medications.

			Calorie prescription					Macronutrient prescription				Food diary			
Trial name	**Study phase**	**Medication**	**Calculation for baseline kcal**	**~500 kcal/d deficit**	**Other**	**Recalculation of kcal restriction based on BMI threshold or timeframe**	**Recalculation with no energy deficit**	**Fat (%)**	**Carbohydrates (%)**	**Protein (%)**	**Dietary pattern**	**Daily**	**3-Day**	**Meal replacements**	**Other tools**
XENDOS	Main	Orlistat	Estimated TEE from self-administered food questionnaire		~800 kcal/d deficit	Every 6 months		30%; < 300 mg of cholesterol			Balanced hypocaloric				
EQUIP	Main	PHEN/TPM		X											
CONQUER	Main	PHEN/TPM		X											
SEQUEL	Extension of CONQUER	PHEN/TPM		X											
SCALE obesity and prediabetes	Main	Liraglutide	TEE[a]	X		BMI ≤ 22 or after 28 weeks of treatment unable to lose additional weight despite BMI ≥ 25	X	30	50	20			Every second month		
	Extension	Liraglutide	TEE[a]	X		BMI ≤ 22 or after 28 weeks of treatment unable to lose additional weight despite BMI ≥ 25	X	30	50	20			Every second month		
SCALE diabetes	Main	Liraglutide	TEE[a]	X		BMI ≤ 22 or after 28 weeks of treatment unable to lose additional weight despite BMI ≥ 25	X	30	50	20			Every second month		
SCALE sleep apnea	Main	Liraglutide	TEE[a]	X				30	50	20			Every 5–8 weeks		
SCALE IBT	Main	Liraglutide			< 200 lbs: 1200 kcal/day; 200–300 lbs: body weight (lb) × 6 (kcal/lb); > 300 lbs: 1800 kcal/day	BMI ≤ 22	X	20–35	45–65	15–20		X			Meal plans
SCALE maintenance	Main: LCD run-in	NA	1200–1400 kcal/d								Meal replacement	X		X	
	Main: RCT of liraglutide versus placebo	Liraglutide	Estimated 24-h energy expenditure	X				30	50	20		X			

(Continues)

TABLE 2 | (Continued)

			Calorie prescription					Macronutrient prescription				Food diary			
Trial name	**Study phase**	**Medication**	**Calculation for baseline kcal**	**~500 kcal/d deficit**	**Other**	**Recalculation of kcal restriction based on BMI threshold or timeframe**	**Recalculation with no energy deficit**	**Fat (%)**	**Carbohydrates (%)**	**Protein (%)**	**Dietary pattern**	**Daily**	**3-Day**	**Meal replacements**	**Other tools**
COR-I	Main	Naltrexone/bupropion	WHO algorithm for calculating resting metabolic rate	X											
COR-II	Main	Naltrexone/bupropion		X											
COR-diabetes	Main	Naltrexone/bupropion	WHO algorithm for calculating resting metabolic rate	X											Exchange lists for weight management booklets
COR-BMOD	Main	Naltrexone/bupropion			≤ 249 lb: 1200 kcal/d; 250–299 lb: 1500 kcal/d; 300–349 lb: 1800 kcal/d; ≥ 350 lb: 2000 kcal/d			≤ 30	50–55	15–20	Balanced deficit diet	X			Calorie counter
STEP 1	Main	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 2	Main	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 3	Main: IBT with LCD + placebo/semaglutide	Semaglutide			1000–1200 kcal/d						Meal replacement	X		X	
	Main: IBT + placebo/semaglutide	Semaglutide			< 200 lbs: 1200 kcal/d; 200–300 lbs: Daily caloric target (kcal) = body weight (lb) × 6 (kcal/lb); > 300 lbs: 1800 kcal/d	BMI ≤ 22.5	X					X			
STEP 4	Main: Semaglutide lead-in	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
	Main: Semaglutide versus placebo	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 5	Main	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 6	Main	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 7	Main	Semaglutide	TEE[a]	X		BMI ≤ 22.5	X					X			
STEP 8	Main	Semaglutide versus	TEE[a]	X		BMI ≤ 22.5	X								

(Continues)

TABLE 2 | (Continued)

			Calorie prescription					Macronutrient prescription				Food diary			
Trial name	**Study phase**	**Medication**	**Calculation for baseline kcal**	**~500 kcal/d deficit**	**Other**	**Recalculation of kcal restriction based on BMI threshold or timeframe**	**Recalculation with no energy deficit**	**Fat (%)**	**Carbohydrates (%)**	**Protein (%)**	**Dietary pattern**	**Daily**	**3-Day**	**Meal replacements**	**Other tools**
		liraglutide													
STEP 9	Main	Semaglutide			Reduced-calorie diet										
STEP 10	Main	Semaglutide			Reduced-calorie diet										
STEP 11	Main	Semaglutide	TEE[a]	X											
STEP HFpEF	Main	Semaglutide			Individualized healthy lifestyle counseling										
STEP-HFpEF DM	Main	Semaglutide			Individualized healthy lifestyle counseling										
STEP UP	Main	Semaglutide	TEE[a]	X											
STEP UP T2D	Main	Semaglutide	TEE[a]	X											
SELECT	Main	Semaglutide			Individualized healthy lifestyle counseling										Guidance documents from steering committee or global experts
SURMOUNT 1	Main	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
	Extension	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
SURMOUNT 2	Main	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20	Healthy, balanced meals		Prior to each counseling visit		Diabetes education
SURMOUNT 3	Main: ILI run-in	N/A			Women: 1200 kcal/d; men: 1500 kcal/d						Meal replacement		Prior to each counseling visit	X	
	Main: RCT of tirzepatide MTD versus placebo	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
SURMOUNT 4	Main: Tirzepatide run-in	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		

(Continues)

TABLE 2 | (Continued)

			Calorie prescription					Macronutrient prescription				Food diary			
Trial name	**Study phase**	**Medication**	**Calculation for baseline kcal**	**~500 kcal/d deficit**	**Other**	**Recalculation of kcal restriction based on BMI threshold or timeframe**	**Recalculation with no energy deficit**	**Fat (%)**	**Carbohydrates (%)**	**Protein (%)**	**Dietary pattern**	**Daily**	**3-Day**	**Meal replacements**	**Other tools**
	Main: RCT of tirzepatide versus placebo	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
SURMOUNT 5	Main	Tirzepatide versus semaglutide	TEE[a]	X		BMI $\leq$ 22		30	50	20			Prior to each counseling visit		
SURMOUNT OSA	Main: Trial 1	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
	Main: Trial 2	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			Prior to each counseling visit		
SURMOUNT CN	Main	Tirzepatide	Total daily energy or (body height (cm)—105) $\times$ 25 kcal/d; thresholds that $\geq$ 1000 kcal for women and $\geq$ 1200 kcal for men	X		BMI $\leq$ 20	X	20–30	40–55	15–20			Prior to each counseling visit		
SURMOUNT J	Main	Tirzepatide	Daily energy intake up to 25 kCal/kg $\times$ standard body weight (as determined by BMI = 22 kg/m^2) for participant BMI $\geq$ 27 kg/m^2; 20–25 kcal/kg $\times$ standard body weight for the participant BMI $\geq$ 35 kg/m^2		Based on JASSO guidelines			20–25	50–60	15–20			Prior to each counseling visit		
SURMOUNT MMO	Main	Tirzepatide	Local standards										NR		
SURMOUNT-maintain	Main: Tirzepatide lead-in	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			NR		
	Main: Tirzepatide	Tirzepatide	TEE[a]	X		BMI $\leq$ 22	X	30	50	20			NR		

(Continues)

TABLE 2 | (Continued)

Trial name	Study phase	Medication	Calorie prescription				Macronutrient prescription			Food diary			
			Calculation for baseline kcal	~500 kcal/d deficit	Other	Recalculation of kcal restriction based on BMI threshold or timeframe	Recalculation with no energy deficit	Fat (%)	Carbohydrates (%)	Protein (%)	Dietary pattern	Daily	3-Day	Meal replacements	Other tools
	5 mg weekly and tirzepatide MTD (10 or 15 mg) versus placebo														
SUMMIT	Main	Tirzepatide													
OASIS 1	Main	Semaglutide (oral)	TEE[a]	X		BMI $\leq$ 22.5 kg/m^2	X					X			
OASIS 2	Main	Semaglutide (oral)	TEE[a]	X		BMI $\leq$ 22.5 kg/m^2	X					X			
OASIS 4	Main	Semaglutide (oral)	TEE[a]	X		BMI $\leq$ 22.5 kg/m^2	X					X			

Abbreviations: BMI = body mass index, BMOD = behavioral modification, COR = Contrave Obesity Research, CPAP = continuous positive airway pressure, D = day, DM = diabetes mellitus, HFpEF = heart failure with preserved ejection fraction, IBT = intensive behavioral therapy, LCD = low-calorie diet, MTD = maximum tolerated dose, NA = not applicable, OASIS = Oral Semaglutide Treatment Effect in People with Obesity, OSA = obstructive sleep apnea, PHEN = phentermine, SCALE = Satiety and Clinical Adiposity- Liraglutide Evidence, SELECT = Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity, STEP = Semaglutide Treatment Effect in People with Obesity, TEE = total daily energy expenditure, TPM = topiramatem, Wk = weeks, XENDOS = XENical in the prevention of diabetes in obese subjects.

[a]TEE (kcal/day) = basal metabolic rate $\times$ 1.3.

thereafter. In the SURMOUNT-3 study, participants underwent a 12-week intensive lifestyle intervention consisting of eight sessions, during which they followed a 1200–1500 kcal/day diet with up to two meal replacements per day and were encouraged to achieve at least 150 min of physical activity per week. Following this phase, participants who achieved at least a 5% greater initial weight loss were randomized to medication or placebo and transitioned to less frequent counseling (every 12 weeks) while maintaining a 500 kcal/day energy deficit and ongoing physical activity.

4 | Discussion

With the novel and highly effective obesity treatments, semaglutide and tirzepatide, the ideal lifestyle intervention that should be paired with OMMs has gained increasing attention [10, 69–72]. In this review we have summarized the diet, physical activity, and behavioral components that have been tested as an adjunct to OMMs in Phase 3 trials. We included 50 reports from 42 Phase 3 studies on orlistat, phentermine/topiramate, liraglutide, naltrexone/bupropion, semaglutide (injectable and oral), and tirzepatide. Some of the most common elements found across trials were the use of dietary goals that promote a 500 kcal/d deficit and physical activity goals of $\geq$ 150 min/week. Other common features included diaries for recording diet and physical activity, and delivery by interventionists who were dieticians or similar qualified healthcare professionals. Many studies provided counseling at least monthly or every 3 months. Several guidelines and papers have highlighted the potential importance of lifestyle, nutritional, and physical activity interventions among individuals prescribed second-generation OMMs [10, 69, 72–76]. Further research is necessary to evaluate various lifestyle interventions combined with OMMs and to assess the effects of different visit frequencies, nutritional strategies, and physical activity recommendations on health outcomes. There remains a significant opportunity to refine lifestyle interventions while also considering both scalability and sustainability. Such efforts may be done in partnership with industry or led by other stakeholders and sectors, such as academia, healthcare systems, food companies, exercise program developers, telehealth, and direct-to-consumer health and wellness companies.

Guidelines for obesity have emphasized that lifestyle modification is the cornerstone of treatment [77]. With behavioral treatment alone, comprehensive interventions that involve similar components such as goal setting and self-monitoring have demonstrated efficacy in numerous clinical trials [78–80]. However, the uptake of lifestyle treatment in primary care remains low. In one study of primary care providers serving Medicare patients, only 1.2% utilized intensive lifestyle treatment for their patients [5]. The low uptake is due to a combination of numerous barriers, such as lack of provider time and resources and insufficient provider knowledge and training in obesity treatment [81–83]. The frequency and content of lifestyle interventions being provided alongside OMMs in real-world settings have not been well quantified.

Across the reviewed studies, few standardized behavioral strategies were used with the exception of self-monitoring strategies such as using pedometers/activity trackers and diet and physical

TABLE 3 | Physical activity components of phase 3 trials of obesity management medications.

			Duration of PA recommended			Type of exercise		Tools	
Study	**Phase**	**Medication**	**≥ 150 min/wk**	**Other target**	**Increase but amount not specified**	**Aerobic**	**Resistance**	**PA diaries**	**Pedometer/activity tracker**
XENDOS	Main	Orlistat		Walking ≥ 1 km/day in addition to usual PA		X		Daily	
EQUIP	Main	PHEN/TPM			X				
CONQUER	Main	PHEN/TPM							
SEQUEL	52-week extension of CONQUER	PHEN/TPM							
SCALE obesity and prediabetes	Main	Liraglutide	X						X
	Extension	Liraglutide	X						X
SCALE diabetes	Main	Liraglutide	X			X			X
SCALE sleep apnea	Main	Liraglutide	X						X
SCALE IBT	Main	Liraglutide		Initial: ≥ 100 min/week (bouts of > 10 min spread across 4–5 days per week); maintenance: ≥ 250 min/week		X			X
SCALE maintenance	Main: LCD run-in	NA	X			X			X
	Main: RCT of liraglutide versus placebo	Liraglutide	X			X			X
COR-I	Main	Naltrexone/bupropion			X				
COR-II	Main	Naltrexone/bupropion			X				
COR-diabetes	Main	Naltrexone/bupropion		30 min/d most days of the week		X			
COR-BMOD	Main	Naltrexone/bupropion		0–6 months: 180 min/wk; months 7–12: 360 min/wk		X	X	Daily	
STEP 1	Main	Semaglutide	X			X		Daily	
STEP 2	Main	Semaglutide	X			X		Daily	

(Continues)

TABLE 3 | (Continued)

Study	Phase	Medication	Duration of PA recommended			Type of exercise		Tools	
			≥ 150 min/wk	Other target	Increase but amount not specified	Aerobic	Resistance	PA diaries	Pedometer/activity tracker
STEP 3	Main: IBT with LCD + placebo/semaglutide	IBT + semaglutide versus IBT + placebo		≥ 100 min/wk spread across 4–5 days and gradually increased to ≥ 200 min/wk		X			
	Main: IBT + placebo/semaglutide	IBT + semaglutide versus IBT + placebo		≥ 100 min/wk spread across 4–5 days and gradually increased to ≥ 200 min/wk		X			X
STEP 4	Main: Semaglutide lead-in	Semaglutide	X			X		Daily	
	Main: Semaglutide versus placebo	Semaglutide	X			X		Daily	
STEP 5	Main	Semaglutide	X			X		Daily	
STEP 6	Main	Semaglutide	X			X		Daily	
STEP 7	Main	Semaglutide	X			X		Daily	
STEP 8	Main	Semaglutide versus liraglutide	X			X		Daily	
STEP 9	Main	Semaglutide			X				
STEP 10	Main	Semaglutide			X				
STEP 11	Main	Semaglutide	X			X			
STEP HFpEF	Main	Semaglutide			X				
STEP-HFpEF DM	Main	Semaglutide			X				
STEP UP	Main	Semaglutide	X			X			
STEP UP T2D	Main	Semaglutide	X			X			
SELECT	Main	Semaglutide							
SURMOUNT 1	Main	Tirzepatide	X					3-day prior to each counseling visit	
	Extension	Tirzepatide	X					3-day prior to each counseling visit	
SURMOUNT 2	Main	Tirzepatide	X			X		3-day prior to each	

(Continues)

TABLE 3 | (Continued)

Study	Phase	Medication	Duration of PA recommended			Type of exercise		Tools	
			≥ 150 min/wk	Other target	Increase but amount not specified	Aerobic	Resistance	PA diaries	Pedometer/activity tracker
								counseling visit	
SURMOUNT 3	Main: ILI run-in	N/A	X			X		3-day prior to each counseling visit	
	Main: RCT of tirzepatide MTD versus placebo	Tirzepatide	X			X		3-day prior to each counseling visit	
SURMOUNT 4	Main: Tirzepatide run-in	Tirzepatide	X					3-day prior to each counseling visit	
	Main: RCT of tirzepatide versus placebo	Tirzepatide	X					3-day prior to each counseling visit	
SURMOUNT 5	Main	Tirzepatide versus semaglutide	X			X		3-day prior to each counseling visit	
SURMOUNT OSA	Main	Tirzepatide	X					3-day prior to each counseling visit	
SURMOUNT CN	Main	Tirzepatide	X					3-day prior to each counseling visit	
SURMOUNT J	Main	Tirzepatide		JASSO guidelines depending on purpose of weight loss (150–420 min)				3-day prior to each counseling visit	
	Main	Tirzepatide		Local standards				NR	

(Continues)

TABLE 3 | (Continued)

Study	Phase	Medication	Duration of PA recommended			Type of exercise		Tools	
			≥ 150 min/wk	Other target	Increase but amount not specified	Aerobic	Resistance	PA diaries	Pedometer/activity tracker
SURMOUNT MMO									
SURMOUNT-maintain	Main: Tirzepatide lead-in	Tirzepatide	X					NR	
	Main: Tirzepatide 5 mg weekly and tirzepatide MTD (10 or 15 mg) versus placebo		X					NR	
SUMMIT	Main	Tirzepatide							
OASIS 1	Main	Semaglutide	X			X		Daily	
OASIS 2	Main	Semaglutide	X			X		Daily	
OASIS 4	Main	Semaglutide	X			X		Daily	

Abbreviations: BMI = body mass index, BMOD = behavioral modification, COR = Contrave Obesity Research, D = day, DM = diabetes mellitus, HFpEF = heart failure with preserved ejection fraction, IBT = intensive behavioral therapy, JASSO = Japan Society for the Study of Obesity, Km = kilometer, LCD = low-calorie diet, Min = minutes, MTD = maximum tolerated dose, NA = not applicable, OASIS = Oral Semaglutide Treatment Effect in People with Obesity, OSA = obstructive sleep apnea, PA = physical activity, PHEN = phentermine, SCALE = Satiety and Clinical Adiposity- Liraglutide Evidence, SELECT = Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity, STEP = Semaglutide Treatment Effect in People with Obesity, TPM = topiramate, Wk = weeks, XENDOS = XENical in the prevention of diabetes in obese subjects.

activity diaries. There are limited data available to assess adherence to these self-monitoring behaviors in the trials reviewed. Most of the trials of OMMs did not include formal obesity treatment curriculums and of these trials that did, most used or adapted materials from the *LEARN Manual*. There is a need to adapt obesity lifestyle treatment protocols to address the unique challenges with OMMs such as side effects, medication adherence, and potential psychosocial issues with clinically significant weight losses. Additionally, most of the recommendations were similar regardless of the co-occurring disease state. Research is necessary to examine the extent of tailoring of lifestyle components for different disease conditions.

One of the most notable evolutions with OMMs compared to lifestyle intervention alone has been the reduced frequency of lifestyle counseling necessary to produce clinically meaningful weight loss. With behavioral obesity treatment alone, a frequency of at least 14 sessions in the first 6 months with continued monthly contact for weight loss maintenance has been considered the standard necessary to produce clinically significant long-term weight losses [5, 6]. Most of the trials of semaglutide and tirzepatide included at least monthly or every 3-month counseling visits. The optimal frequency of counseling is needed as well as consideration of the cadence. In addition, lifestyle modification may improve other outcomes beyond weight loss such as dietary quality, cardiorespiratory fitness, and mitigation of muscle and bone loss, and these outcomes should be measured and considered in future trials. Given the constraints in many clinical settings, achieving monthly or more frequent visits during dose titration or every 3-month counseling may be difficult and require innovations to obesity care pathways.

Future studies are needed to examine how to scale and sustain lifestyle interventions provided with OMMs. Digital health platforms, telemedicine, and group-based coaching models may expand reach and reduce the burden on clinical staff, enabling more efficient delivery of comprehensive care. A growing number of direct-to-consumer platforms (e.g., Ro, WeightWatchers, Omada Health, and Noom) have been developed and may help to bridge this gap. Some direct-to-consumer platforms provide prescriptions for FDA-approved medications and others have provided compounded medications. Many direct-to-consumer programs are delivered via telehealth and vary in the amounts and types of lifestyle treatment. e.g., some platforms offer initial consultations with a provider to facilitate access to OMMs, on-demand health coaching and provider access, apps, recipes and educational resources, messaging and care support, tools to track progress, ongoing medication management, and workshops. However, evidence is needed to demonstrate the efficacy of such programs as well as mechanisms to integrate with healthcare systems to avoid care fragmentation.

In addition, sustained use of obesity medications also depends on their cost-effectiveness, including whether insurance covers them and how much coverage is provided, the availability of supportive features such as lifestyle programs or digital tools, and payment models that make long-term treatment affordable [84]. Similar to challenges encountered with bariatric surgery,

TABLE 4 | Behavioral modification approaches used in phase 3 trials of obesity management medications.

			Frequency of lifestyle counseling					Counselors		Mode of delivery		Mode of delivery		
Study	**Phase**	**Medication**	**Weekly to every 3 Wk**	**Every 4 Wk/ monthly**	**Every 8 Wk**	**Every 12–13 Wk**	**Frequency of diet/ exercise goal review**	**Dietician/ similar qualified healthcare professional**	**Other**	**Individual**	**Group**	**In-person**	**Remote**	**Treatment manual**
XENDOS	Main	Orlistat	Mon 0–6: Every 2 wk	After 6 mon: Monthly										
EQUIP	Main	PHEN/TPM					Monthly							*LEARN Manual*
CONQUER	Main	PHEN/TPM					Monthly							*LEARN Manual*
SEQUEL	52-week extension of CONQUER	PHEN/TPM		X										*LEARN Manual*
SCALE obesity and prediabetes	Main	Liraglutide		X				X		X	X			
	Extension	Liraglutide		X				X		X	X			
SCALE diabetes	Main	Liraglutide		X Except wk 50 and 56 (6 wk apart)				X		X	X			
SCALE sleep apnea	Main	Liraglutide		X										
SCALE IBT	Main	Liraglutide	Mon 0–1: Weekly Mon 2–6: Every 2 wk	Mon 7–13: Monthly				X		X		X	X	Adapted from diabetes prevention program
SCALE maintenance	Main: LCD run-in	N/A	Weekly						Nutritionist			X	X	
	Main: RCT of liraglutide versus placebo	Liraglutide	Wk 0–4: Weekly	Wk 6–52: Every 4 wk					Nutritionist			X		
COR-I	Main	Naltrexone/ bupropion				X								
COR-II	Main	Naltrexone/ bupropion				X								

(Continues)

TABLE 4 | (Continued)

Study	Phase	Medication	Frequency of lifestyle counseling				Frequency of diet/ exercise goal review	Counselors		Mode of delivery		Mode of delivery		Treatment manual
			Weekly to every 3 Wk	Every 4 Wk/ monthly	Every 8 Wk	Every 12–13 Wk		Dietician/ similar qualified healthcare professional	Other	Individual	Group	In-person	Remote	
COR-diabetes	Main	Naltrexone/ bupropion		Baseline and wk 4		After wk 4: Every 12 wk			Study site personnel					Written instructions on behavioral modification
COR-BMOD	Main	Naltrexone/ bupropion	Wk 0–16: Weekly Wk 16–28: Every other wk	After wk 28: Monthly				X			X	X		Materials from *LEARN* program, diabetes prevention program, other handouts from authors
STEP 1	Main	Semaglutide		X				X				X	X	
STEP 2	Main	Semaglutide		X				X				X	X	
STEP 3	Main: IBT with LCD + placebo/ semaglutide	Semaglutide	Wk 0–12: Weekly Wk 12–24: Every other wk	After wk 24: Every 4 wk				X				X	X	X
	Main: IBT + placebo/ semaglutide	Semaglutide		X				X				X	X	
STEP 4	Main: Semaglutide lead-in	Semaglutide		X				X				X	X	
	Main: Semaglutide versus placebo	Semaglutide		X				X				X	X	
STEP 5	Main	Semaglutide		X				X				X	X	
STEP 6	Main	Semaglutide		X				X				X	X	
STEP 7	Main	Semaglutide		Every 4–6 wk				X				X	X	
STEP 8	Main	Semaglutide versus liraglutide		Every 4–6 wk				X				X	X	
STEP 9	Main	Semaglutide		Wk 0–20: Every 4 wk	After wk 20: Every 8 wk			X						

(Continues)

TABLE 4 | (Continued)

Study	Phase	Medication	Frequency of lifestyle counseling				Frequency of diet/ exercise goal review	Counselors		Mode of delivery		Mode of delivery		Treatment manual
			Weekly to every 3 Wk	Every 4 Wk/ monthly	Every 8 Wk	Every 12–13 Wk		Dietician/ similar qualified healthcare professional	Other	Individual	Group	In-person	Remote	
STEP 10	Main	Semaglutide		Wk 0–20: Every 4 wk	After wk 20: Every 8 wk			X		X				
STEP 11	Main	Semaglutide		X				X				X	X	
STEP HFpEF	Main	Semaglutide		Wk 0–20: Every 4 wk	After wk 20: Every 8 wk					X				
STEP-HFpEF DM	Main	Semaglutide		Wk 0–20: Every 4 wk	After wk 20: Every 8 wk					X				
STEP UP	Main	Semaglutide		X				X				X	X	
STEP UP T2D	Main	Semaglutide		X				X				X	X	
SELECT	Main	Semaglutide		Wk 0–20: Every 4 wk Wk 20–26: Every 6 wk		After wk 26: Every 13 wk						X	X	
SURMOUNT 1	Main	Tirzepatide		Wk 0–12: Every 4 wk		After wk 12: Every 12 wk	Every 4 wk	X				X	X	
	Extension	Tirzepatide				X	Every 6–7 wk	X				X	X	
SURMOUNT 2	Main	Tirzepatide		Wk 0–24: Every 4 wk		After wk 24: Every 12 wk	Every 4 wk	X				X	X	
SURMOUNT 3	Main: ILI run-in	N/A	Wk 0–5: Weekly Wk 6–12: Every 2 wk				Wk −12, −11, −10, −9, −8, −6, −4, −2, 0	X				X		

(Continues)

TABLE 4 | (Continued)

Study	Phase	Medication	Frequency of lifestyle counseling				Frequency of diet/ exercise goal review	Counselors		Mode of delivery		Mode of delivery		Treatment manual
			Weekly to every 3 Wk	Every 4 Wk/ monthly	Every 8 Wk	Every 12–13 Wk		Dietician/ similar qualified healthcare professional	Other	Individual	Group	In-person	Remote	
	Main: RCT of tirzepatide MTD versus placebo	Tirzepatide				X	Every 4 wk	X				X	X	
SURMOUNT 4	Main: Tirzepatide run-in	Tirzepatide		Wk 0–12: Every 4 wk		After wk 12: Every 12 wk	Every 4 wk	X				X	X	
	Main: RCT of tirzepatide versus placebo	Tirzepatide				X	Every 4 wk	X				X	X	
SURMOUNT 5	Main	Tirzepatide versus semaglutide		Wk 0–12: Every 4 wk		After wk 12: Every 12 wk	Every 4 wk	X				X	X	
SURMOUNT OSA	Main	Tirzepatide		X			Every 4 wk		Study personnel experienced in diet/ exercise counseling					
SURMOUNT CN	Main	Tirzepatide		Wk 0–12: Every 4 wk		After wk 12: Every 12 wk	Every 4 wk	X				X	X	
SURMOUNT J	Main	Tirzepatide		Wk 0–12: Every 4 wk		Wk 24, 36, 48, 52, and 60 through 72 wk	Every 4 wk	X						
SURMOUNT MMO	Main	Tirzepatide		Wk 0–24: Every 4 wk		After wk 24: Every 12 wk		X				X	X	
SURMOUNT-maintain	Main: Tirzepatide lead-in	Tirzepatide		NR				X						
	Main: Tirzepatide 5 mg weekly and tirzepatide MTD (10 or 15 mg) versus placebo			NR				X						

(Continues)

TABLE 4 | (Continued)

Study	Phase	Medication	Frequency of lifestyle counseling				Frequency of diet/ exercise goal review	Counselors		Mode of delivery		Mode of delivery		Treatment manual
			Weekly to every 3 Wk	Every 4 Wk/ monthly	Every 8 Wk	Every 12–13 Wk		Dietician/ similar qualified healthcare professional	Other	Individual	Group	In-person	Remote	
SUMMIT	Main	Tirzepatide												
OASIS 1	Main	Semaglutide	Wk 0–4: Every 2 wk	After Wk 4: Every 4 Wk				X				X	X	
OASIS 2	Main	Semaglutide	Wk 0–4: Every 2 wk	After Wk 4: Every 4 Wk				X				X	X	
OASIS 4	Main	Semaglutide	Wk 0–4: Every 2 wk	After Wk 4: Every 4 Wk				X				X	X	

Abbreviations: BMOD = behavioral modification, COR = Contrave Obesity Research, DM = diabetes mellitus, HFpEF = heart failure with preserved ejection fraction, IBT = intensive behavioral therapy, LCD = low-calorie diet, Mon = month(s), MTD = maximum tolerated dose, OASIS = Oral Semaglutide Treatment Effect in People with Obesity, OSA = obstructive sleep apnea, PHEN = phentermine, SCALE = Satiety and Clinical Adiposity- Liraglutide Evidence, SELECT = Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity, STEP = Semaglutide Treatment Effect in People with Obesity, TPM = topiramate, Wk = weeks, XENDOS = XENical in the prevention of diabetes in obese subjects.

insurance plan features such as lack of insurance coverage, high patient costs and copays, and strict prior authorization criteria remain barriers to treatment utilization [85]. To address these challenges, various payment frameworks have been explored, such as value-based insurance design, which has been proposed as a model for bariatric surgery to address healthcare spending and also to foster high-value services [86, 87]. Within value-based payment models, lifestyle intervention may play a critical role in maximizing the clinical and economic value of OMMs by enhancing outcomes and supporting long-term adherence and maintenance [88]. Workforce training is also critical to ensure providers are equipped to manage pharmacotherapy alongside behavioral interventions. Ultimately, sustainable models will require collaboration among healthcare systems, payers, employers, and community organizations to ensure integrated, scalable care that adapts as treatment landscapes and patient needs evolve.

Similar to guidelines for behavioral treatment alone [89–91], the lifestyle interventions provided with OMMs have focused primarily on caloric restriction. Previous studies testing dietary interventions alone have examined various macronutrient permutations and dietary patterns [92]. However, promoting adherence to facilitate a caloric deficit has been recognized as the greatest strategy to achieve weight loss. In the reviewed studies, most included very similar dietary prescriptions with an emphasis on attaining calorie reduction. Many plans also included a recommendation of 20% protein. Reduction in muscle mass has been a growing concern with the use of OMMs [93]. Increased protein intake may help attenuate the effects of these medications on muscle mass loss, though this has largely been extrapolated from lifestyle interventions as well as bariatric surgery [10]. e.g., a meta-analysis of 28 trials found that increased protein intake significantly prevented muscle mass decline, though it did not significantly prevent decreases in muscle strength and physical function [94]. More research is necessary to ascertain specific recommendations for protein intake. In addition, changes in other dietary components such as fiber, calcium and other micronutrients have also not been well delineated in trials. Further research is necessary to determine the optimal dietary plan for individuals taking OMMs.

The physical activity prescriptions provided in most trials were $\geq$ 150 min/week, aligning with general public health guidelines from the Physical Activity Guidelines for Americans. These guidelines advised adults to engage in at least 150 min/week of moderate-intensity aerobic activity (i.e., activity that requires 3.0 to $<$ 6.0 METs), such as brisk walking [95]. Few studies recommended that participants specifically increase resistance exercise. This highlights a significant gap in the literature, suggesting the need for future studies to more precisely examine how different types, frequencies, and durations of physical activity may complement and potentiate intervention effects.

Limitations of this review include that we extracted data based on what was published in the article or available in the study protocol. The descriptions of the lifestyle interventions were often brief and similar across trials testing the same medication. We were unable to conduct a meta-analysis of the efficacy of various lifestyle components such as frequency of lifestyle intervention due to the potential confound of the type of medication; for example, the majority of trials providing counseling sessions every 3 months were testing tirzepatide. In addition, we only included evidence of what has been provided in Phase 3 clinical trials. Further research is needed to assess lifestyle interventions that are being provided in real-world settings. There were insufficient data available on participant adherence to self-monitoring, session attendance, dietary change, and physical activity. These data should be systematically collected and reported in future trials.

5 | Conclusion

Current OMMs are approved as adjuncts to reduced-calorie diets and physical activity. This review focused on the lifestyle interventions that have been provided as part of Phase 3 trials of OMMs. It addresses an issue of significant clinical relevance because of the increased uptake of these medications as well as their growing use in different fields. More research is needed to examine different lifestyle interventions paired with OMMs and to test the impacts of different frequencies, nutritional and physical activity recommendations and the influence on health outcomes. A significant opportunity remains to optimize lifestyle interventions while balancing scalability and sustainability.

Author Contributions

Ariana M. Chao: conceptualization. All authors contributed to the literature review, writing, and revision of the manuscript. All authors approved the final version.

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Conflicts of Interest

A.M.C. has served on advisory boards to Eli Lilly and Company, Novo Nordisk, and Boehringer Ingelheim and received grant support from Eli Lilly and Company on behalf of the University of Pennsylvania and Johns Hopkins University.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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