Cost-effectiveness analysis of five anti-obesity medications from a US payer's perspective

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Abstract *Background and aims:* To determine the cost-effectiveness of anti-obesity medications (AOM): tirzepatide, semaglutide, liraglutide, phentermine plus topiramate (PpT), and naltrexone plus bupropion (NpB).
Methods and results: From a U.S. perspective we developed a Markov model to simulate weight change over a 40-year time horizon using results from clinical studies. According to the body mass index (BMI), cardiovascular diseases, diabetes and mortality risk were the health states considered in the model, being mutually exclusive. Costs of AOM, adverse events, cardiovascular events, and diabetes were included. We applied a 3% per-year discount rate and calculated the incremental cost-effectiveness ratios (ICERs) of cost per quality-adjusted life-year (QALY) gained. Probabilistic sensitivity analyses incorporated uncertainty in input parameters. A deterministic analysis was conducted to determine the robustness of the model. The model included a cohort of 78.2% females with a mean age of 45 years and BMI of 37.1 (SD 4.9) for females and 36.8 (SD 4.9) for males. NpB and PpT were the least costly medications and, all medications differed no more than 0.5 QALYs. Tirzepatide ICER was $355,616 per QALY. Liraglutide and semaglutide options were dominated by PpT.
Conclusion: Compared to other AOM, PpT was lowest cost treatment with nearly identical QALYs with other agents.
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1. Introduction

1.1. Obesity

Obesity is an endocrinological and preventable disease defined as having a body mass index (BMI) of 30 or greater [1]. Almost a third of the world's population is obese and, in the U.S., it is expected that over half the population will be obese by 2030 [1,2]. The aggregate medical cost of obesity in the U.S. was $260 billion in 2016 (1.5% of the gross domestic product), equating to 20% of all health care expenditures [1,3].

Obesity etiology is multifactorial and has been related to environmental, behavioral, and biological factors [1]. Obesity has been associated with severe medical conditions such as type 2 diabetes, cardiovascular diseases, and respiratory disease (i.e., sleep apnea) [1,4]. Furthermore, obesity has been related to various cancers, including gastrointestinal, thyroid, breast, and ovarian cancer [5]. In addition, obesity is related to many psychiatric disorders (e.g., depression, anxiety, etc.) and affects patients' quality of life by reducing physical activity and increasing the risk of detrimental health outcomes. Studies show that achieving a 5% reduction in weight loss provides a significant health benefit [6].

1.2. Treatments

Non-pharmacologic therapies are the primary interventions for weight reduction. However, limitations exist with these therapies. While health care systems recommend lifestyle modification through community-based obesity management programs, the long-term success of these programs remains limited [7,8]. Surgical intervention (i.e., bariatric surgery) is an option for qualifying patients with a BMI ≥ 40; however, this treatment introduces surgical risks and can lead to severe nutritional deficiencies, like dumping syndrome and other gastric complications and some patients rebound and gain weight after the intervention [9,10].

The FDA-approved phentermine plus topiramate (PpT) in 2012 as an appetite reducer; however, safety concerns about this therapy remain [11]. Naltrexone plus bupropion (NpB) as a combination for obesity treatment was approved by the FDA in 2014 and acts by promoting satiety, reducing food intake and enhancing energy expenditure. More recently, the glucagon-like peptide 1 receptor agonists (GLP-1), such as dulaglutide, liraglutide, and semaglutide, which are used to treat diabetes, have shown an additional benefit of weight reduction; this is also true for the recently approved tirzepatide [12]. Given the variable effectiveness of weight management programs and future obesity estimates, pharmacological therapies for obesity should be sought and health plans and policymakers should consider reimbursement or pricing strategies that may improve access to these therapies.

The application of cost-effective therapies has the potential to improve population health and decrease unnecessary economic burden. BMI reduction has been shown to improve patients' health conditions and reduce medical expenditures [13,14]. Assuming a weight reduction of ≥5% is needed for therapies to achieve the desired outcomes, policymakers are in a unique position to identify the most cost-effective therapy for obesity treatment and evaluate the potential benefits these treatments pose to the healthcare system [15,16]. Therefore, the purpose of this study was to conduct a cost-effectiveness analysis comparing five antiobesity medications (AOM) from a U.S. payer's perspective.

2. Methods

We developed a decision analytic Markov model to estimate the cost-effectiveness of five different AOMs (semaglutide, liraglutide, PpT, NpB and, tirzepatide) from a U.S. payer's perspective. This manuscript follows the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) (see supplemental file for complete checklist) [17].

3. Base case scenario

The base case study population were adults with a mean age of 45 years and comprised of 78.2% females. The represented in this model is an average of the patient population from the five medications' clinical trials [18–31]. BMI distribution and sex was estimated using the National Health and Nutritional Examination Survey (NHANES) from 2018 [32]. The initial simulated cohort had a mean BMI of 37.1 (standard deviation (SD) 4.9) for females and 36.8 (SD 4.9) for males.

3.1. Comparators

Five AOMs were compared. These included three GLP-1 AOM, semaglutide (Wegovy®), liraglutide (Saxenda®) and tirzepatide (Mounjaro™), though this last has no indication for obesity management; and two drug combinations, one of which is an amphetamine and antiepileptic − phentermine plus topiramate (PpT, Qsymia™), and the other a combination of an opioid antagonist and antidepressant with an anorexigenic effect − naltrexone plus bupropion (NpB, Contrave®) [33–37].

The efficacy and safety data for each AOM were extracted from randomized controlled trials (see Table 1) [18–31]. Each AOM has different clinical trials, but only those conducted with weight loss as the main outcome and that had a duration of 20 weeks or longer were selected to estimate a weighted average of the efficacy of each AOM. Measures of variance, if missing from original reports, were obtained by contacting the manufacturers. For the discontinuation branch the treatment discontinuation rate for each AOM was the weighted average from the selected studies, regardless of the reason. We considered that this rate could estimate the real-world probability of discontinuation. In this branch, the average rate of severe adverse events (SAE) for each AOM was utilized to estimate the likelihood and cost of experiencing a SAE.

Life style modification is always the first step to approach obesity [16]. However, the effectiveness of life style modification on weight reduction and long term maintenance have been showed to be brief and minimal [38]. Patients considering AOM or undergoing bariatric surgery are require additional interventions to life style modifications, and these modifications might always be part of the therapy [16]. Because all AOM are studied in conjunction with lifestyle modifications and nutritional interventions, these treatments were not included

Table 1 Model inputs.

Antiobesity Medication	Effectiveness	Probability of 5% weight loss	Prob. of a SAE	Prob. of Treatment Discontinuation	References[a]	Weekly cost ($)[b]
Semaglutide	−13.5 (9.6)	0.58	0.09	0.12	[18–21]	236.1
Liraglutide	−8.5 (6.9)	0.47	0.06	0.23	[21–24]	236.1
PpT	−10.2 (8.7)	0.50	0.04	0.31	[25–27]	34.9
NpB	−7.7 (7.7)	0.46	0.01	0.37	[28–30]	53.1
Tirzepatide	−20.9 (12.2)	0.60	0.05	0.22	[31]	170.5

Prob. Probability.
SAE severe adverse event.
PpT phentermine plus topiramate.
NpB naltrexone plus bupropion.
[a] Data provided is a weighted average of the reported in the references listed.
[b] Prices are 2021 US dollars ($) and 30% discount applied. All drug prices have been retrieved from: Red Book (Micromedex®, n. d.).

separately in the comparison. Bariatric surgery, a surgical intervention, was not included as a comparator because it is limited to individuals experiencing extreme obesity. Moreover, pharmacologic treatment is often warranted after surgical intervention [10].

3.1.1. Model

A Markov model with a one-year cycle length was chosen to appropriately reflect the underlying nature of obesity as a chronic condition and its long-term effects (see Fig. 1) using the BMI categories as defined by the Centers for Disease Control and Prevention (CDC): normal BMI < 18.5, overweight BMI 18.5 to <25, and obesity range BMI => 30.0 [14]. Participants had no comorbidities when entering the model. Patients entering the model had the probability of continuing on treatment (persistence branch) or not (discontinuation branch). Patients discontinuing and patients not experiencing weight loss (proportion of clinical trial participants who did not achieve at least a 5% body weight reduction) were assumed to maintain their weight the first year followed by a yearly increase of their BMI based on epidemiological studies [39]. In contrast, patients experiencing at least 5% of body weight loss may reduce long-term risk by moving from one BMI-related health state to another. Within each BMI-related health state, patients could experience a cardiovascular event (acute
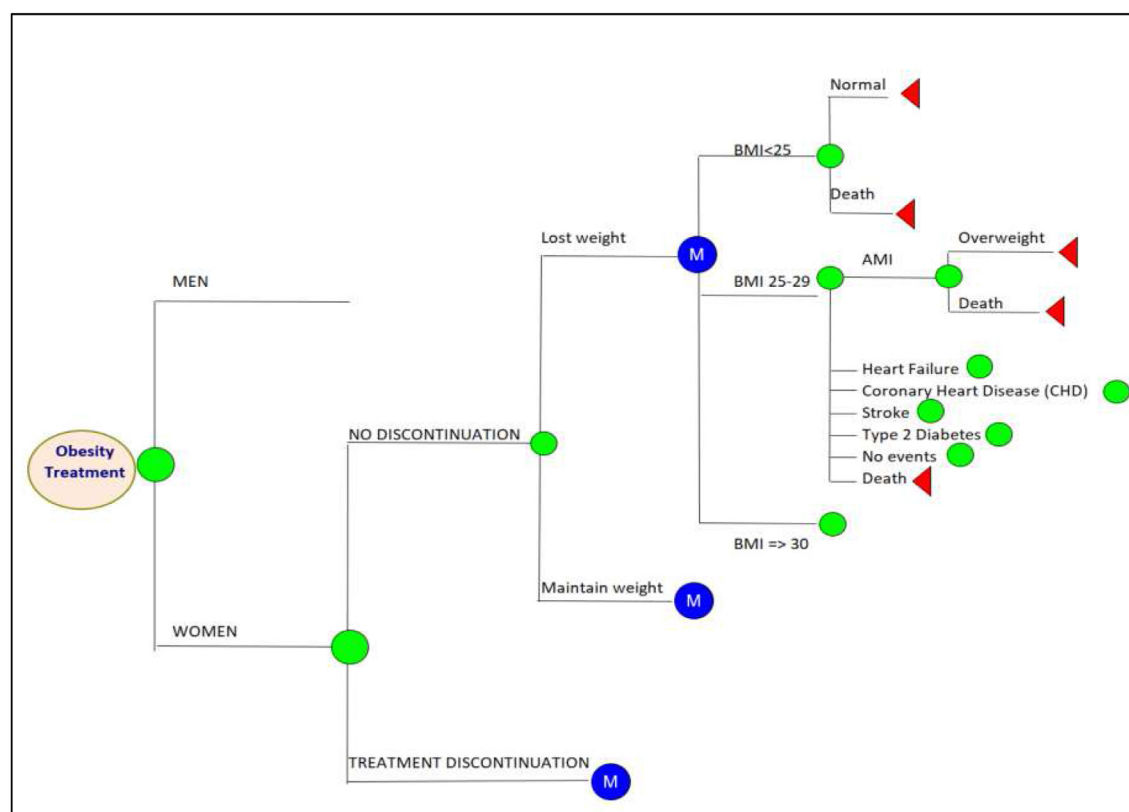

Figure 1 Markov model decision tree for the obesity treatments. BMI body mass index.

myocardial infarction (AMI), coronary heart disease (CHD), congestive heart failure (CHF) or stroke), or develop diabetes. The assumption for this model is that patients experiencing weight reduction can consequently change BMI categories, thereby reducing the risk of obesity-related complications as seen in previous studies, while those not experiencing any weight reduction or discontinuing the medication would increase their body weight through the years [39].

3.2. Time horizon & discount rate

A 40-year time horizon approach was selected for this model with a globally accepted 3% discount rate. Obesity has been considered a long-term disease, and it is assumed that discontinuing pharmacology treatment could lead to rebound or non-improvement, i.e. not losing weight [40]. In the STEP4 clinical trial comparing semaglutide maintenance therapy to placebo after a period of pharmacologic treatment, weight gain was observed in patients who discontinued therapy, and different studies have shown different regain rates after stopping AOM medications [20,41]. We assume life time therapy for those successful (patients experiencing at least 5% of body weight loss).

3.3. Choice of health outcomes

Although obesity has been linked to many negative outcomes, we focused primarily on cardiovascular effects and diabetes, due to the substantial evidence suggesting their correlation and the relative impact on health compared to

other long-term implications such as joint replacement or cancer [4,42]. The excess risk of experiencing these cardiovascular events, developing diabetes or dying was obtained by sex, age and overweight or obese status from the van Baal et al. study, as reported in their supplementary material (Table 1s, sheets 5−11) [43]. We considered this health states mutually exclusive, so we did not use an added risk once experiencing a cardiovascular event or developing diabetes.

3.4. Estimating utilities and costs

The model utilities, dis-utilities, as well as the event costs, are shown in Table 2. AOM costs in U.S. dollars ($) were obtained from the Red Book using wholesale acquisition costs (Table 1) [44]. These costs were discounted by 30% to account for manufacturer rebates and discounts that are now common in the US marketplace. This cost-effectiveness study considered only direct cost, this is costs on the AOM treatments and the health states from a payer's perspective were included. The model included the total cost of the AOM, SAE, the selected cardiovascular complications of obesity and diabetes, and the excess cost of being overweight or obese. Cost of diabetes was from a 2017 report from the American Diabetes Association and for cardiovascular outcomes from the study of Bress et al. [45,46]. No cost for death was included in the analysis. The average cost of a SAE was included independently of the specific adverse event, considering the cost of severe ones [47]. For each SAE, the model assumed an average side effect duration of 2 months, with the cost and disutility adjusted accordingly.

Table 2 Utilities and dis-utilities for the model.

Utilities	Female	Male	References	Cost[a] Mean (SD)	References
BMI normal	1		[49]		
BMI overweight	0.94		[49]	677 (70)	Ward et al., 2021
BMI obese	0.875		[49]	1930 (110)	Ward et al., 2021
Acute Myocardial Infarction	−0.026		[75]	25,721 (4459)	[46]
50−64				25,570 (4766)	
65−84				6156 (4361)	
≥85					
Coronary Heart Disease	−0.06	−0.04	[50]	8429 (511)	[46]
50−64				8648 (444)	
65−84				6528 (531)	
≥85					
Congestive Heart Failure	−0.07	−0.09	[50]	12,990 (1331)	[46]
50−64				11,874 (1336)	
65−84				10,161 (1592)	
≥85					
Stroke	−0.31		[50]	18,881 (16,760)	[46]
50−64				14,500 (11,708)	
65−84				11,759 (6509)	
≥85					
Diabetes	−0.08		[50]	7757	[45]
<65				15,384	
≥65					
Serious Adverse Event	−0.04		[51]	24,546 (1483)	[47]

BMI body mass index.
SD standard deviation.
  [a] Cost in 2021 US dollars ($).

All costs retrieved from literature were converted to November 2021 dollars using a conversion factor estimated from the U.S. Bureau of Labor Statistics (Medical care in U.S. city average, all urban consumers, not seasonally adjusted) [48].

BMI utilities were obtained from the Rothberg et al. study [49]. Data for utilities of cardiovascular events included in the model (AMI, CHD, CHF and stroke) were obtained from the literature as well as for diabetes and utility for SAE [50,51].

3.5. Analytical methods

Total costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were estimated for each AOM. The base case was identified as the lowest total cost product. A willingness to pay (WTP) threshold of $150,000 per QALY was used to determine the most cost-effective treatment as have been used in previous studies. A 10,000 MonteCarlo simulation was performed with a WTP threshold of $150,000 per QALY (range from 0 to $500,000) for the probabilistic analysis, the uncertainty of the results was expressed using a cost-effectiveness acceptability curve (CEAC). To assess parameters' uncertainty of the model we conducted a one-way sensitivity analysis, the analysis was based on the net monetary benefit framework and was focused/included on all comparators. This model was constructed and analyzed using TreeAge Pro Healthcare 2021 (©2021 TreeAge Software, Inc.).

4. Results

Over a lifetime horizon, the treatment with the lowest cost was PpT ($118,900), followed by NpB ($126,957). Semaglutide was the most costly treatment ($308,767). All the compared treatments had similar QALYs; tirzepatide had the highest QALYs (29.550) and, NpB had the lowest (29.223). To see the complete cost-effectiveness and ICER results, see Table 3. PpT was the most cost-effective option, dominating NpB, semaglutide and liraglutide. Tirzepatide's ICER relative to PpT was $355,616 per QALY.

One-way sensitivity analysis was performed to examine the robustness of the inputs. The model was more sensitive to the utility and cost of being obese (BMI => 30) and to the prices of tirzepatide, PpT, semaglutide, and liraglutide per week, in this order. The cost of stroke and diabetes were also among the most relevant variables for the model, as shown in the tornado diagram (Fig. 2). To see the complete sensitivity analysis results, see Supplemental

Table 1s. To achieve a cost-effectiveness ratio of $150,000, the weekly price of tirzepatide would need to be $91.70, which means a 37.6% discount from its current price.

A probabilistic sensitivity analysis (PSA) over the lifetime horizon was performed with the cost-effectiveness analysis probability curve shown in Fig. 3. PpT was the optimal choice across a wide range of WTP values up to $400,000 per QALY. Above this boundary tirzepatide had the highest probability of being cost-effective followed by PpT. Neither of the other GLP-1 receptor agonists were considered to be cost-effective.

5. Discussion

Our analysis found PpT to be the most cost-effective AOM option among the five available treatments in a healthy population. NpB is dominated by PpT; liraglutide and semaglutide are also dominated as they lie above the efficiency frontier. However, all treatments produced similar QALYs.

While there are differences across the clinical studies concerning to weight loss, the amount of weight loss for these agents was insufficient to result in patients moving from one BMI category to another. Thus, only modest differences across the products were observed in terms of QALYs.

Our model focuses on the cardiovascular outcomes related to obesity and the risk of developing diabetes. The AOMs for our model are indicated to be used in obese patients (BMI ≥ 30) or overweight individuals (BMI > 27) with at least one additional comorbidity as an adjunct to a reduced-calorie diet and increased physical activity, though the patients entering our model had no cardiovascular disease or diabetes and the BMI was a distribution, so patients with BMI < 25 could also receive one of the AOM. Previous diabetes and obesity models have been developed to assess outcomes other than cardiovascular and diabetes [52]. We considered that different obesity-related outcomes, such as knee replacement, cancer, fatty liver disease, and sleep apnea, pose a relatively small risk, and, for some of them a clear relationship with obesity has not been well established. Therefore, we did not include them in our model despite their inclusion in other models [53−55].

Previous studies have focused on comparing different lifestyle programs, pharmacologic treatments, or bariatric surgery to elucidate the most cost-effective option to treat obesity, mainly from a payer's perspective [53,56−58]. However, long-term achievement of weight loss with

Table 3 Cost, effectiveness and Incremental Cost-Effectiveness Ratio (ICER).

AOM	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
Phentermine plus topiramate	$118,900		29.226		
Naltrexone plus bupropion	$126,957	$8057	29.223	−0.003	−$2,656,171
Tirzepatide	$234,084	$115,184	29.550	0.324	$355,616
Liraglutide	$252,146	$133,246	29.229	0.003	$39,665,285
Semaglutide	$308,767	$189,867	29.233	0.008	$24,274,467

Tornado Diagram - Net Monetary Benefits (WTP: 150,000)

Figure showing horizontal bars for the following parameters (top to bottom):
- utility of being obese (BMI=> 30)
- cost of tirzepatide per week
- cost of PpT per week
- cost of semaglutide per week
- cost of liraglutide per week
- cost of being obese (BMI=>30)
- cost of NpB per week
- cost of stroke
- probability of being female
- cost of diabetes
- utility of being overweight (BMI 25-29)
- cost of being overweight (BMI 25-30)

EV: 4,264,948
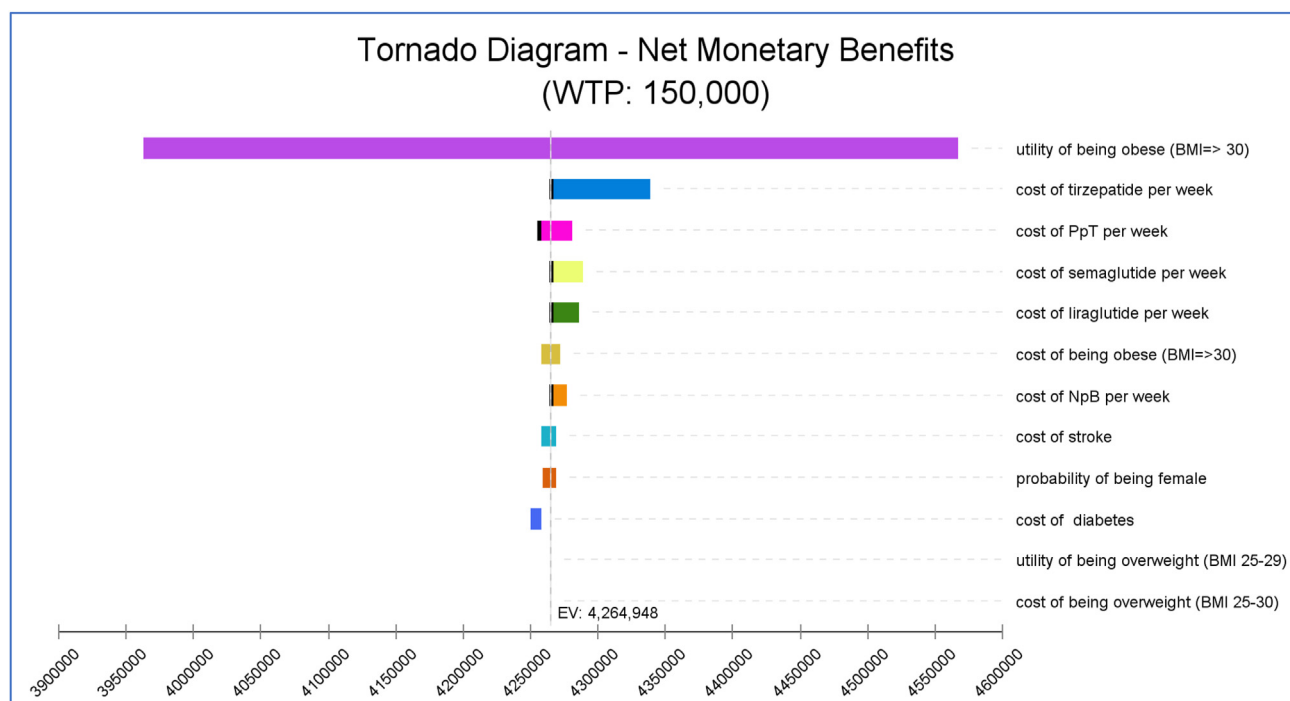
X-axis: 3900000 to 4600000

Figure 2 Deterministic Analysis for the Net Monetary Benefit (all comparators), WTP Willingness to Pay, BMI Body Mass Index, PpT Phentermine plus Topiramate, NpB Naltrexone plus Bupropion.

neither lifestyle nor pharmacologic treatments or bariatric surgery has been established [7,59].

As part of a validation and to ensure the mathematical relationship were accurate, a series of sensitivity analysis were conducted to ensure the findings were logical and consistent with the evidence. All authors as well as other faculty reviewed the model structure and results as part of a face validity assessment. We also compared our model to
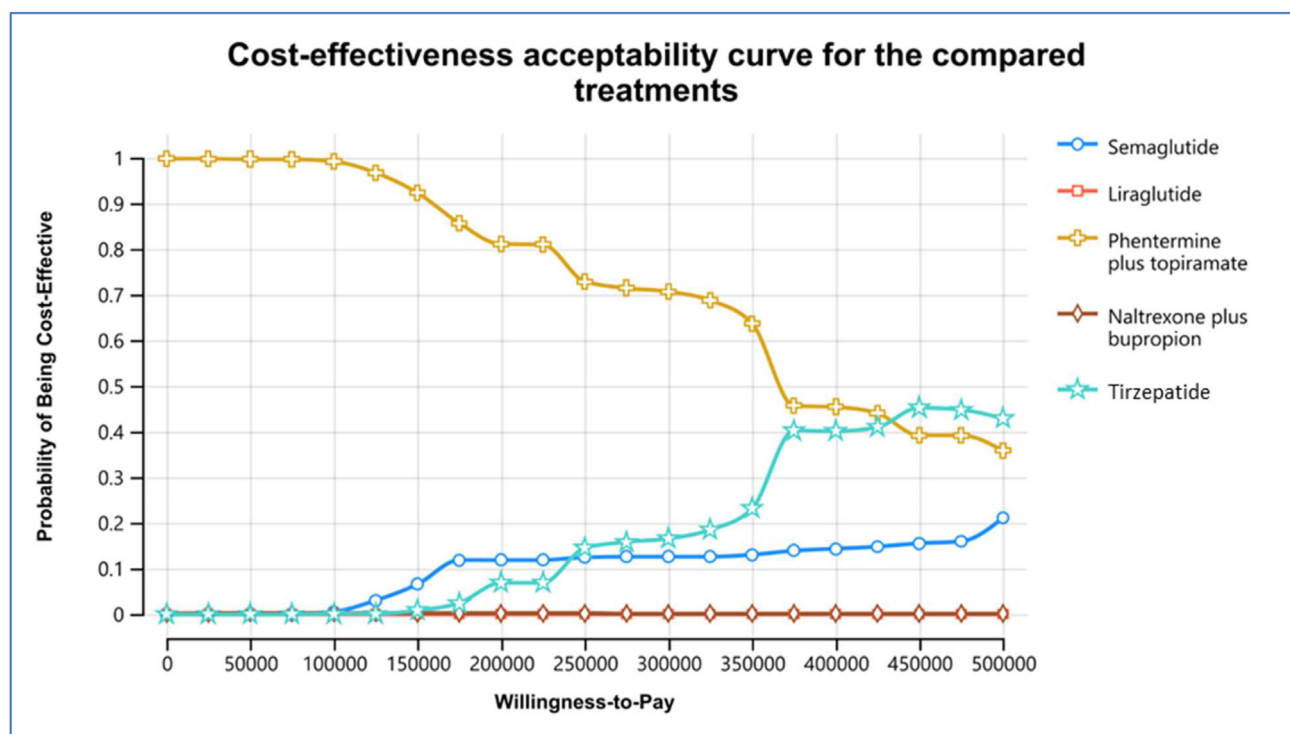
Cost-effectiveness acceptability curve for the compared treatments

Graph plotting Probability of Being Cost-Effective (y-axis, 0 to 1) vs Willingness-to-Pay (x-axis, 0 to 500000) for:
- Semaglutide
- Liraglutide
- Phentermine plus topiramate
- Naltrexone plus bupropion
- Tirzepatide

Figure 3 Cost-Effectiveness Acceptability Curve for the compared treatments, Liraglutide and Naltrexone plus Bupropion lines are overlapped.

published similar analyses, conducted using similar in population, setting, perspective and treatments compared [56,58,60–62]. However, these analyses were different from our analysis in that they included other health states of cancer, sleep apnea and bariatric surgery. Furthermore, we account for mortality risk in the normal BMI health state and, excess risk of mortality by the different events in the overweight and obese health states. Kim et al. account for mortality by age and BMI stratification. Finally, previous analyses using a 30-year time horizon, whereas the time horizon in our analysis was 40 years.

From a U.S payer's perspective, several pharmacoeconomic studies have compared AOMs, though none currently has included tirzepatide [53,56,58,60–63]. Among these, PpT has been shown to be the preferred option compared to medication and life style programs. The high price of semaglutide is why it is not the preferred option [58]. However, semaglutide, when compared only to other GLP-1 therapies, has been shown to be the most cost-effective option [60]. A recently published analysis comparing the 4 FDA-approved AOMs for obesity in our study found semaglutide to be the most cost-effective option, which differs from the findings of the Institute for Clinical and Economic Review's 2022 report comparing the same AOMs, which found PpT to be the most cost-effective option [61,62]. Kim et al.'s cost economic study time horizon contemplated 30 years for patients initiating at age 46 and included not only cardiovascular conditions and diabetes but cancer as well. Meanwhile, the ICER report did not include cancer, osteoarthritis, joint surgery, or sleep apnea as separate Markov states in their model. The estimated total QALYs in these two studies are lower than our analysis, but the incremental differences between treatments is similar. With all these results there are no clear conclusions for policymakers and payers to implement a decision on coverage for the most cost-effective therapy. However, due to its higher price, semaglutide was not the most cost-effective therapy in our analysis.

There was inconsistency across the selected studies regarding the reporting of SAEs. In the case of NpB, Wadden et al. reported only two severe drug-related adverse events with no other information on SAEs [29]. This accounted for the lowest rate of SAEs among all AOMs compared. A meta-analysis of unpublished clinical data of NpB trials showed a higher rate of SAEs (12%) [64]. A meta-analysis of drug discontinuation due to adverse events showed no significant difference between NpB, PpT, and liraglutide [65]. In our model, NpB had the highest probability of discontinuation for any reason (0.37 NpB compared to 0.12 for semaglutide).

Our study has several limitations that should be kept in mind when interpreting the results. First, we assume that all patients entering the cohort do not have diabetes, prediabetes, or any cardiovascular comorbidity (e.g. hypertension, diabetes, dyslipidemia, etc.) when only approximately 30% of the obese patients are healthy and these conditions have been linked with obesity and an increased risk of cardiovascular outcomes [66,67]. We also did not account for the increased risk of patients once experienced a cardiovascular event or developing diabetes; therefore, no increase in risk was added when transitioning through the Markov model. Second, we used a lifetime horizon considering that obesity is a chronic disease, as some published studies have shown that stopping the AOM can increase body weight [21]. We assume that those patients who experienced discontinuation or treatment failure would gain weight through the years, as has been previously published [1,20,40]. We only could include the recently published results for tirzepatide as a treatment for obesity. However, the drug has not been approved to treat obesity, and in our model, the reduction of BMI by tirzepatide was the most impactful [37]. Finally, whether these AOMs would have long-term adverse outcomes that would modify the model has not yet been established, so no long-term adverse events were included [68].

Despite the high prevalence of obesity in the U.S., it is not widely recognized as a disease, and health care systems and providers have identified several barriers to its treatment [69]. Among these barriers are the lack of motivation, the low rates of patient commitment to a weight loss management plan, and the low rates of AOM prescription [69,70]. This poor use may also be justified by the limited insurance coverage of these AOMs, with less than a third of the U.S. insurance companies covering these medications. If they are covered, there may also be some restrictions on their use because pharmacotherapy was not included in the Affordable Care Act while lifestyle modification plans and bariatric surgery were in 2010 [71]. A study analyzing 136 marketplace health insurance plans showed that just 11% had some coverage for AOM [72]. The field of obesity therapy continues to expand with not only new medications gaining access to the market but, the development of immunotherapy. For these reasons, these treatments should be encouraged in a country with 40% of its population obese [73,74].

6. Conclusion

Even if all the pharmacologic treatments compared have shown efficacy in clinical trials, there are no significant differences in QALYs compared to PpT. PpT is the most cost-effective treatment, mainly because of its low price and similar effectiveness. Our study provided evidence for payers to support decision-making on AOM coverage.

Ethics

No data have been collected for this study. The study is secondary research conducted using already published data.

Authors contributions

AGL has participated developing the study protocol and research design, data acquisition, analysis and interpretation of the results and drafted the manuscript. **MST** participated in developing the study protocol and research design, analyzed data, and contributed to interpretation

the data. She also reviewed and edited the manuscript. **LVZ** participated in developing the research design and interpretation of the results. He has reviewed and edited the manuscript. **SI** has participated in interpreting results and reviewed the final manuscript. **JC** has participated developing the study protocol, data acquisition, and reviewed the manuscript. **DCM** supervised the study and drafted the study protocol and research design, guided the analysis of the data, provided interpretation as well as reviewed and edited the manuscript.

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Data availability statement

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

Declaration of competing interest

There are no competing financial interests in relation to the work described. All the authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.03.012.

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