

The Value of Weight Loss: Cost-Effectiveness of Modern Anti-Obesity Medications for Clinical and Policy Decisions

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ABSTRACT

Background: Obesity is a chronic, relapsing, multifactorial disease associated with type 2 diabetes, cardiovascular disease, sleep apnea, osteoarthritis, chronic kidney disease, cancer, reduced quality of life, and increased healthcare expenditure. These drugs produce clinically meaningful weight loss and cardiometabolic improvement, but their high acquisition costs have created major concerns for patients, payers, and health systems.

Objective: This review evaluates the cost-effectiveness of pharmacologic treatments in adults with overweight or obesity, with emphasis on recent evidence informing the American College of Physicians' living guideline.

Methods: Recent evidence supports a major shift from prolonged injectable-containing regimens toward six-month and nine-month all-oral regimens based on bempicicline, bupropion, linezolid, moxifloxacin, delamanid, clofazimine and fluoroquinolones where appropriate.

Results: The cost-effectiveness evidence base remains limited by low-quality studies and heterogeneity in assumptions, time horizons, prices, treatment discontinuation, weight regain, and downstream disease modeling.

Conclusion: Pharmacologic obesity treatment should not be evaluated only by short-term weight loss, but by durable health gain, affordability, prevention of obesity-related complications, and budget impact.

Keywords: obesity, type 2 diabetes, cardiovascular disease, sleep apnea, chronic kidney disease, cancer

1. INTRODUCTION

Obesity is now recognized as a chronic disease rather than a simple lifestyle problem. It results from complex interactions among genetics, neuroendocrine regulation, food systems, physical activity environments, sleep, medication exposure, social determinants, psychological stress, and metabolic adaptation [1]. The economic burden is substantial because obesity increases the risk of type 2

diabetes, hypertension, dyslipidemia, cardiovascular disease, fatty liver disease, osteoarthritis, infertility, depression, and several cancers. For many years, pharmacologic obesity treatment had limited clinical use because older drugs produced modest weight loss, had tolerability problems, or raised safety concerns. The therapeutic landscape has changed with newer agents, especially semaglutide and tirzepatide, which can produce weight loss approaching outcomes previously associated mainly with procedural interventions [2]. A 2025 *Nature Medicine* systematic review and network meta-analysis identified 56 randomized trials involving 60,307 participants and reported that all obesity management medications produced significantly greater total body weight loss than placebo, with semaglutide and tirzepatide producing more than 10% total body weight loss on average. However, clinical effectiveness alone is not enough [3]. A treatment can be highly effective but still difficult to fund at population level if its cost is very high, if treatment must continue indefinitely, or if benefits reverse after discontinuation. This is why cost-effectiveness has become central to obesity pharmacotherapy decisions. The American College of Physicians issued a 2026 living clinical guideline based on systematic reviews of pharmacologic treatment in adults with overweight or obesity, reflecting how fast this evidence base is changing [4]. This review synthesized recent evidence on the cost-effectiveness of pharmacologic treatments for adults with overweight or obesity. The review focuses on drugs used with lifestyle modification, including semaglutide, tirzepatide, liraglutide, phentermine-topiramate, naltrexone-bupropion, and orlistat. It also discusses the 2026 ACP systematic review, recent pharmacoeconomic studies, major methodological limitations, clinical implications, and policy directions.

2. MATERIALS & METHODS

This narrative review was developed using recent research published mainly from 2021 to 2026. Priority was given to systematic reviews, health economic evaluations, network meta-analyses, guideline-linked reviews, and studies relevant to U.S. payer or international health-system decision-making. Key search concepts included “obesity pharmacotherapy,” “cost-effectiveness,” “semaglutide,” “tirzepatide,” “phentermine-topiramate,” “naltrexone-bupropion,” “orlistat,” “quality-adjusted life-years,” “incremental cost-effectiveness ratio,” and “American College of Physicians.” An article was also considered because it discusses obesity, mood, metabolic health, and metformin’s possible role in behavioral adherence and metabolic outcomes; however, it was used only as supportive background rather than as primary economic evidence [5].

3. CURRENT PHARMACOLOGIC OPTIONS FOR OBESITY

Pharmacologic treatment is usually considered for adults with body mass index of at least 30 kg/m², or at least 27 kg/m² with weight-related comorbidity, alongside lifestyle intervention. The main currently discussed agents include:

Table 01: Main currently discussed agents

Drug/class	Main mechanism	Key strength	Key limitation
Semaglutide 2.4 mg	GLP-1 receptor agonist	Large weight loss and cardiometabolic benefit	High cost, gastrointestinal adverse effects, long-term use needed
Tirzepatide	Dual GIP/GLP-1 receptor agonist	Very large weight loss; strong diabetes prevention potential	High cost, long-term real-world affordability concerns
Liraglutide 3.0 mg	Daily GLP-1 receptor agonist	Established evidence base	Daily injection, less weight loss than semaglutide/tirzepatide

Phentermine-topiramate	Sympathomimetic + anticonvulsant	Lower cost; effective weight loss	Teratogenic risk, cardiovascular/psychiatric cautions
Naltrexone-bupropion	Opioid antagonist + antidepressant	Lower cost; may help appetite/craving pathways	Nausea, blood pressure concerns, contraindications
Orlistat	Gastrointestinal lipase inhibitor	Low systemic exposure	Modest efficacy, gastrointestinal adverse effects

The major health economic question is not simply which drug causes the greatest weight loss. The more important question is which treatment gives the best balance of cost, quality-adjusted life-years, adverse effects, adherence, diabetes prevention, cardiovascular risk reduction, and long-term affordability.

4. EVIDENCE FROM THE ACP COST-EFFECTIVENESS REVIEW

The 2026 ACP systematic review by Jenniskens and colleagues evaluated cost-effectiveness of pharmacologic treatments for adults with overweight or obesity in a U.S. setting. The review searched MEDLINE, Embase, and economic databases through October 13, 2025, and focused on non-industry-sponsored U.S. trial-based and model-based cost-effectiveness evaluations. The review's overall conclusion was cautious: existing cost-effectiveness evidence is hampered by poor study quality, which limits firm conclusions [6]. This is important because many economic models depend heavily on assumptions about drug price, treatment duration, weight regain after stopping treatment, quality-of-life improvement, adverse effects, cardiovascular benefit, diabetes prevention, and long-term adherence. Small changes in these assumptions can significantly change whether a treatment appears cost-effective [7].

5. COST-EFFECTIVENESS OF NEWER INCRETIN-BASED THERAPIES

SEMAGLUTIDE

Semaglutide 2.4 mg has transformed obesity treatment because it produces large average weight loss and improves several cardiometabolic markers. Economic studies, however, show mixed conclusions because drug acquisition cost is high. Some country-specific models have found semaglutide cost-effective under certain assumptions, especially where drug prices are lower or where long-term reductions in diabetes and cardiovascular disease are heavily weighted [8]. A 2023 pharmacoeconomic review summarized several semaglutide cost-effectiveness analyses and listed studies from the United Kingdom, the United States, and Canada, including semaglutide 2.4 mg models. However, model conclusions depend strongly on local price, payer perspective, and time horizon. In high-price markets, semaglutide often fails to meet conventional willingness-to-pay thresholds unless substantial price discounts are applied.

TIRZEPATIDE

Tirzepatide generally produces greater average weight loss than semaglutide in clinical trials and has strong potential to prevent diabetes and cardiovascular disease. A 2025 *JAMA Health Forum* economic evaluation estimated that, per 100,000 eligible U.S. adults, tirzepatide would avert more obesity cases, diabetes cases, and cardiovascular disease cases than semaglutide. However, the same study found that tirzepatide and semaglutide had high incremental cost-effectiveness ratios at current U.S. net prices. Specifically, the study estimated incremental cost-effectiveness ratios of \$197,023 per QALY for tirzepatide and \$467,676 per QALY for semaglutide [9]. To reach a \$100,000 per QALY threshold, prices

would need further discounts of 30.5% for tirzepatide and 81.9% for semaglutide. This finding is highly policy-relevant: the most effective drugs may still not be affordable or cost-effective at current prices when offered broadly to large populations.

6. COST-EFFECTIVENESS OF OLDER AND LOWER-COST AGENTS

PHENTERMINE-TOPIRAMATE

Phentermine-topiramate is generally less expensive than GLP-1-based therapies and can produce clinically meaningful weight loss. Because cost is lower, it may be economically attractive even if average weight loss is less than with tirzepatide or semaglutide. However, safety considerations are important [10]. It is not suitable for all patients, especially those with pregnancy potential without reliable contraception, uncontrolled hypertension, certain cardiovascular risks, or relevant psychiatric concerns.

NALTREXONE-BUPROPION

Naltrexone-bupropion is another lower-cost option. In the 2025 JAMA Health Forum analysis, naltrexone-bupropion was estimated to be cost-saving because of its lower cost and had an 89.1% probability of being cost-effective at \$100,000 per QALY. This does not mean it is clinically superior. Rather, it shows how price strongly affects cost-effectiveness [11]. A drug with modest effect can appear economically favorable if it is inexpensive, while a highly effective drug can appear economically unfavorable if it is very expensive.

ORLISTAT

Orlistat has modest efficacy and common gastrointestinal adverse effects, but it is comparatively inexpensive and has minimal systemic exposure. It may be relevant where injectable incretin therapies are unaffordable or unavailable. Still, its lower efficacy and tolerability limitations reduce its clinical appeal for many patients [12].

7. COMPARATIVE INTERPRETATION OF ECONOMIC EVIDENCE

Table 02: The economic evidence can be summarized as follows

Treatment	Clinical weight-loss effect	Cost-effectiveness profile	Best-fit population
Tirzepatide	Highest among current options	Strong health gains but often not cost-effective at current U.S. prices	High-risk patients, especially diabetes prevention/cardiometabolic risk
Semaglutide 2.4 mg	Very high	Often price-sensitive; may require major discounts	Patients needing large weight loss with obesity complications
Liraglutide 3.0 mg	Moderate to high	Less attractive now because newer drugs are more effective	Patients unable to use weekly agents
Phentermine-topiramate	Moderate to high	Potentially favorable due to low price	Carefully selected adults without contraindications
Naltrexone-bupropion	Moderate	May be cost-saving in some models	Patients with craving-related eating patterns and no contraindications
Orlistat	Modest	Low cost but limited effectiveness	Patients preferring non-systemic oral therapy

This comparison shows that cost-effectiveness is not the same as clinical effectiveness. Semaglutide and tirzepatide are clinically powerful, but affordability and budget impact remain major barriers.

8. MAJOR DRIVERS OF COST-EFFECTIVENESS

DRUG PRICE

Drug price is the most important driver. High annual prices can overwhelm downstream savings from reduced diabetes, cardiovascular disease, and healthcare utilization. The *JAMA Health Forum* model showed that even large projected reductions in obesity-related complications did not make semaglutide or tirzepatide cost-effective at current U.S. prices without substantial discounts [13].

TREATMENT DURATION

Obesity is chronic, so stopping treatment often leads to weight regain. Economic models that assume short treatment duration with permanent benefit may overestimate cost-effectiveness. Models that assume lifelong therapy may produce very high lifetime costs [14]. A realistic approach must include partial weight regain, discontinuation, switching, and re-initiation.

BASELINE RISK

Cost-effectiveness improves when treatment is targeted toward people at high risk of costly complications. For example, a patient with obesity, prediabetes, hypertension, fatty liver disease, and sleep apnea is more likely to gain measurable economic benefit from effective pharmacotherapy than a lower-risk patient with uncomplicated class I obesity [15].

QUALITY-OF-LIFE GAINS

Weight loss can improve mobility, pain, sleep, mood, fertility, stigma-related distress, and daily functioning. However, quality-of-life gains are difficult to measure consistently, and different economic models assign different utility values to weight loss [16].

ADHERENCE AND PERSISTENCE

Real-world medication persistence is often lower than clinical trial persistence. If patients discontinue early because of side effects, cost, access barriers, or injection burden, expected benefits decline. Economic models that use trial adherence may overestimate real-world cost-effectiveness.

9. VALUE-ADDED FRAMEWORK FOR CLINICAL DECISION-MAKING

A stronger approach is to allocate pharmacologic treatment based on clinical need, expected benefit, safety, patient preference, and economic value.

Proposed risk-based prescribing model

- Confirm obesity as a chronic disease requiring long-term care. Avoid framing medication as a short cosmetic intervention [17].
- Assess baseline cardiometabolic risk. Prioritize patients with prediabetes, type 2 diabetes, cardiovascular disease risk, hypertension, dyslipidemia, fatty liver disease, sleep apnea, or severe obesity.
- Select medication by benefit-risk-cost profile. The most expensive drug should not automatically be first choice for every patient.

- Use response-based continuation. Continue therapy when weight loss, metabolic improvement, and tolerability justify cost.
- Plan for long-term maintenance. Include lifestyle support, nutrition therapy, physical activity, sleep, behavioral care, and follow-up [18].
- Use shared decision-making. Discuss cost, side effects, expected weight loss, stopping rules, and long-term affordability.

10. EQUITY AND POLICY CONSIDERATIONS

The arrival of highly effective obesity medications creates a major equity challenge. Patients with private insurance or personal financial resources may access semaglutide or tirzepatide, while lower-income patients may be limited to older drugs or no pharmacologic therapy. This is ethically concerning because obesity prevalence and obesity-related complications are often higher in socially disadvantaged groups. Policy decisions should therefore consider not only cost-effectiveness ratios but also budget impact, fairness, access, and prevention of long-term health disparities. Price negotiation, outcome-based reimbursement, step-therapy protocols, and risk-based eligibility criteria may help balance access with affordability.

11. ROLE OF PSYCHOLOGICAL AND METABOLIC COMORBIDITY

Obesity often coexists with depression, anxiety, emotional eating, cognitive burden, and reduced quality of life. A review discussed obesity's relationship with mood, cognitive performance, metabolic dysfunction, and the possible supportive role of metformin in improving metabolic and psychological functioning [19]. Although this article is not a cost-effectiveness study of modern anti-obesity drugs, it adds useful context: pharmacologic obesity care should not focus only on body weight, but also on mood, adherence, metabolic health, and behavioral sustainability.

12. METHODOLOGICAL PROBLEMS IN CURRENT COST-EFFECTIVENESS STUDIES

Table 03: The current economic literature has several weaknesses:

Problem	Why it matters
Short trial horizons	Long-term complications may be missed
Uncertain weight regains assumptions	Benefits may be overstated or understated
Variable drug prices	Results may not transfer across countries
Industry influence in some models	Risk of optimistic assumptions
Limited head-to-head evidence	Comparative value remains uncertain
Weak real-world adherence data	Trial-based benefits may not reflect practice
Inconsistent utility estimates	QALY calculations vary widely
Limited equity analysis	Cost-effectiveness may ignore access disparities

The 2026 ACP-linked review's cautious conclusion is therefore appropriate. The evidence is promising, but not yet strong enough to support simple universal claims about which drug is always most cost-effective.

13. FUTURE RESEARCH PRIORITIES

Future studies should focus on:

- Long-term real-world cost-effectiveness beyond 5–10 years.

- Head-to-head economic evaluations of tirzepatide, semaglutide, phentermine-topiramate, and naltrexone-bupropion.
- Cost-effectiveness in high-risk subgroups, including prediabetes, cardiovascular disease, sleep apnea, and severe obesity.
- Weight regains and treatment discontinuation models based on real-world evidence.
- Country-specific analyses using actual negotiated prices.
- Patient-reported outcomes, productivity, disability, and quality-of-life gains.
- Equity-focused models that assess access and affordability across socioeconomic groups.
- Budget impact studies for national insurance systems and public payers.

14. CONCLUSION

Pharmacologic obesity treatment is entering a new era. Semaglutide and tirzepatide provide major clinical benefits and may prevent diabetes and cardiovascular disease, but their current prices limit cost-effectiveness in broad population use. Lower-cost agents such as naltrexone-bupropion and phentermine-topiramate may be economically attractive for selected patients, although their efficacy and safety profiles differ. The 2026 ACP systematic review appropriately highlights that available cost-effectiveness evidence remains limited by low-quality studies and uncertain modeling assumptions. The best policy approach is not unrestricted prescribing or complete restriction, but risk-adapted, value-based treatment. Patients with the highest clinical risk and greatest expected long-term benefit should be prioritized, while payers and policymakers should pursue price reductions, real-world evidence generation, and equitable access strategies. Ultimately, the cost-effectiveness of obesity pharmacotherapy depends not only on kilograms lost, but on durable health gains, affordability, patient-centered outcomes, and prevention of costly obesity-related complications.

AUTHOR CONTRIBUTION STATEMENT

Rohan Mehta & Priya Nair: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Trial Registration: Trial registration is not applicable to this study, as it does not involve clinical trials, human participants, or experimental interventions.

Generative AI Disclosure: Generative artificial intelligence tools were not used for generating research data, conducting analyses, or producing scientific conclusions in this study. The authors take full responsibility for the content and accuracy of the manuscript.

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SUPPLEMENTAL MATERIAL

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.