REVIEW ARTICLE

Cost-effectiveness analysis of Oral Semaglutide treatment for type 2 diabetes mellitus patients: a systematic review

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ABSTRACT

GLP-1 is a new generation of antidiabetics recommended by the American Diabetes Association and European Association for the study of diabetes as an add-on therapy for metformin when therapeutic purposes are not achieved. In this context, oral Semaglutide received FDA approval in September 2019 to be used alongside dietary and exercise regimens to enhance glycemic management in adults diagnosed with type 2 diabetes mellitus (T2DM). Therefore, this systematic review aimed to analyze cost-effectiveness of oral Semaglutide compared to other antidiabetics and/or injectable GLP-1 within the same group. Three databases namely Scopus, ScienceDirect, and PubMed were used for the literature search. Preferred Reporting Items for Systematic Review (PRISMA) guidelines were used to select the studies based on the inclusion and exclusion criteria. Quality assessment was carried out using CHEERS 2022, while the decision on cost-effectiveness was determined using the willingness-to-pay thresholds stated in each study. The results showed that from the initial search yielding 240 studies, 12 met the inclusion criteria. Oral Semaglutide was considered cost-effective compared to SGLT2 and DPP4 inhibitors, as well as injectable GLP-1 due to its higher effectiveness and lower cost. However, it was not cost-effective compared to biguanide/conventional therapy due to the higher cost. The primary sources of uncertainty in the studies were identified as time horizon, discount rate, cost, and treatment policy estimand. In conclusion, the development of oral Semaglutide represents a significant advancement in antidiabetic medications. This systematic review showed that oral Semaglutide appeared to be more cost-effective compared to other antidiabetic medications for T2DM.

Key words:
pharmacoeconomic; cost-effectiveness; oral GLP-1; Oral Semaglutide; type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus is considered a significant global health issue with an increase in patients each year. Data from the International Diabetes Federation (IDF) stated that in 2021, there were 529 million patients worldwide with diabetes mellitus.[1] Moreover, Lin et al. projected an increase in both mortality and prevalence from 1990-2025.[2]

From a healthcare perspective, Type 2 Diabetes Mellitus (T2DM) has a significant impact on economic burden. Economic evaluation is a crucial aspect of providing evidence on the economic merit of new medications, which helps policymakers prioritize limited healthcare resources. The economic burdens of T2DM appear to increase healthcare costs and decrease economic development, with the major expenditure being medicines. Both direct and non-direct medical costs for T2DM are significant and increasing over time.[3] Therefore, it is important to emphasize efficiency and effectiveness in healthcare costs. An effective method to analyze cost and help policymakers select rational medicines is cost-effectiveness analysis. This method provides an overview of the best therapy recommendation with the lowest cost for T2DM therapy.

There are various T2DM therapies, ranging from first-line treatments (Sulfonylurea, Biguanide) to newer generations, such as Glucagon-like Peptide 1 (GLP-1). The mechanism of GLP-1 comprises pancreas stimulation to produce more insulin after eating and help maintain blood glucose levels. Oral GLP-1, the newest form was recommended by the American Diabetes Association and European Association for the study of diabetes as an add-on therapy for metformin when therapeutic purposes are not achieved. In this context, oral Semaglutide received FDA approval in September 2019 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is also the first oral GLP-1 approved based on phase 3, randomized pioneer trials.[4]

Other reviews have focused only on the effectiveness of oral Semaglutide, but none have reviewed cost-effectiveness[4,5]. Therefore, this systematic review aimed to analyze the cost-effectiveness of oral Semaglutide compared to other antidiabetics and/or injectable GLP-1 in the same group. The results can support policy decisions regarding the use of oral Semaglutide, while also contributing to the development and enhancement of future Cost-Effectiveness Analyses (CEAs).

METHODS

Study Selection

This systematic review focused on cost-effectiveness of T2DM therapy using oral Semaglutide. The study selection process included filtering titles and abstracts before evaluating quality based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Literature Search Strategy

The literature review comprised relevant studies published between 2019-2023. Databases such as PubMed, ScienceDirect, and Scopus were used for the literature search. The search was concentrated on “Cost-effectiveness Oral Semaglutide for type 2 diabetes mellitus”, using strategic searching with Boolean operators such as “AND” and “OR”. The inclusion and exclusion criteria for this research were selected using the following search technique based on the Participants, Intervention, Comparator, Outcome, and Study Design (PICOS) criteria as follows:

a. Inclusion criteria

- Studies published between 2019 and 2023.
- Studies meeting the PICOS criteria:
  1. Participants: Adults with Type 2 Diabetes Mellitus
  2. Intervention: Oral Semaglutide treatment.
  3. Comparator: Other antidiabetic drugs, such as SGLT-2i, DPP-4i, GLP-1, and other standard care.
  4. Outcome: Cost, Quality Adjusted Life Years (QALY) and/ clinical outcomes such as HbA1c% reduction, and Incremental Cost-Effective Ratio (ICER) value.
  5. Study design: cost-effectiveness analysis.
- Studies published in English.

b. Exclusion criteria
- Studies on specific populations such as pregnancy patients, those with type 1 diabetes mellitus (T1DM), prediabetes, unspecified diabetes types, or a combination of T2DM and T1DM were removed from consideration.
- Review studies.

Data Extraction/Analysis

In the initial step, studies were selected according to the established inclusion and exclusion criteria. Subsequently, summary tables and figures of these characteristics were constructed. Conclusions regarding the cost-effectiveness of the intervention were gathered and categorized into four classes, namely "yes" (cost-effective), "no" (not cost-effective), "sometimes" (only cost-effective in specific subgroups), and "no conclusion" (cannot determine cost-effectiveness due to limited data). To assess whether an intervention would qualify as cost-effective, Incremental Cost-Effectiveness Ratios (ICERs) were juxtaposed with the specified willingness-to-pay thresholds outlined in each study.

Quality Assessment Reporting

Quality assessment reporting used the 28-item checklist from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) available on the ISPOR (Improving Healthcare Decision) website. Each "yes" response was given a score of 1, while "no or not applicable" received a score of 0. The quality of studies was categorized as high, moderate, or poor based on total scores including high with a score of 22 to 28 (over 75%), moderate with a score ranging from 14 to 21 (50% to 75%), and poor with a score < 14 (below 50%).

RESULTS

General Characteristics Of The Included Studies

Based on the results, the initial search yielded 240 studies, with 14 being duplicated. After screening titles and abstracts for exclusion criteria, 211 studies were excluded. Subsequently, screening for eligibility was carried out leaving only 12 studies eligible for review (Figure. 1).

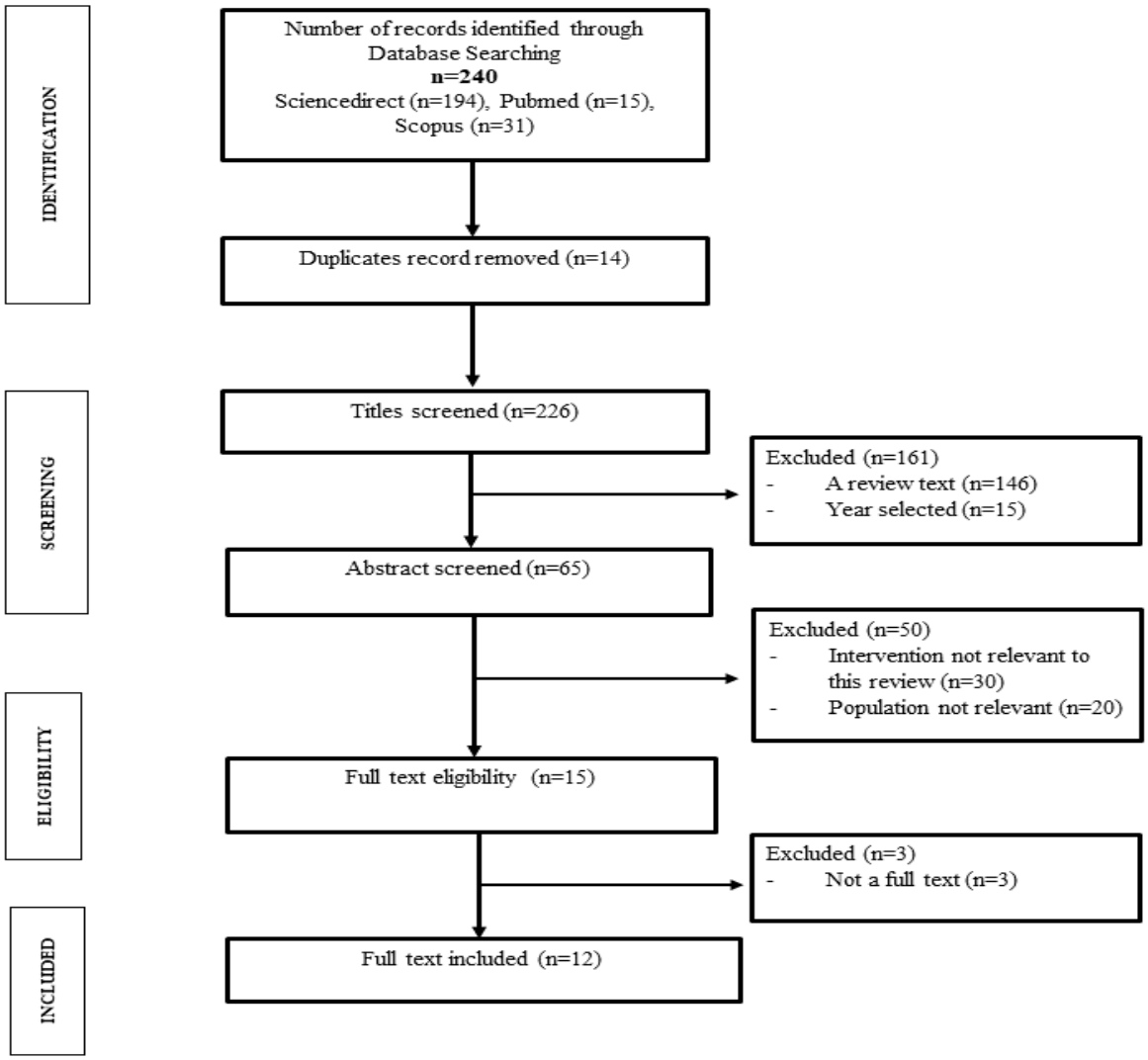

Figure 1. PRISMA Flowchart

The general characteristics of the included studies are shown in Table 1. All studies were conducted in high-income countries, with eight in Europe (one in Portugal, three in the United Kingdom, two in Denmark, one in Sweden, and one in the Netherlands), three in the United States of America, and one in China. Furthermore, all studies compared GLP-1 with at least one comparator and used economic models to examine the relative cost-effectiveness. The most frequently used models were IQVIA Core Diabetes Model (CDM) version 9 (*n*=5), and Markov Model (*n*=2), followed by the United Kingdom Prospective Diabetes Study Outcome Model version 2.1 (*n*=1), Hypothetical cohort of adults with T2DM and inadequate HbA1c control with 1 to 2 OADs (*n*=1), decision tree (*n*=1), and Microsoft Excel for Office 365 v.1911 (*n*=1). Seven studies used a payer perspective, two studies used a societal perspective, and four studies used a provider perspective. One study adopted a short-term time horizon (one year), and the remaining used a 30-year time horizon, with almost all using a lifetime time horizon (50 years). The population of all studies consisted of adult patients with T2DM and HbA1c scores between 7,5%-10,5%, with a

Body Mass Index of over 33 kg/m². The common comparators to oral GLP-1 were SGLT2i (*n*=10), DPP-4i (*n*=6), Biguanide (*n*=3), and injectable/subcutaneous GLP-1 (*n*=6).

Quality Assessment

Table 3 shows the quality assessment results, with all studies indicating good quality according to the CHEERS checklist (scores ranging between 22 and 28). Four studies did not include parameters, such as population status. Two studies omitted summaries of the main results, such as the summary of cost, effectiveness, and ICER. One study did not provide information regarding the effect of engagement with patients and others affected. However, all studies incorporated in the review carried out sensitivity analyses.

Economic Evaluation Results

Table 2 summarizes the economic outcomes observed in the included studies. A total of 11 studies concluded that oral GLP-1 showed more cost-effectiveness than the comparator, while 1 study reported otherwise. All studies showed dominance when compared to injectable/subcutaneous GLP-1, with lower cost and higher effectiveness. Discounted rates ranging from 1.5% to 5% per annum were used in all studies, and costs were determined according to the perspective used. From a provider or payer perspective, only direct medical cost was considered, while studies conducted from a societal perspective included both direct and indirect medical costs.

Table 1. General Characteristics of the Included Studies

Country	First author, year	Comparison (Oral Semaglutide vs Treatment B)	Model	Perspective	Time Horizon	Participants (disease condition and/or medications)
Portugal	Malkin *et al.,* 2022[7]	Empagliflozin (SGLT-2i), Dulaglutide (GLP-1)	IQVIA Core Diabetes Model (V.9.0)	Payer	50-year	Adult patients and have duration diabetics for 7 years and have HbA1c over 7%
Netherlands	Malkin *et al*., 2021[8]	Empagliflozin (SGLT-2i), Sitagliptin (DPP-4i), Injectable Liraglutide (GLP-1)	IQVIA Core Diabetes Model (V.9.0)	Societal	30-year	Adult patients
United States of America	Choi *et al*., 2022[9]	2021 ADA/EASD guidelines	Individual-level Monte Carlo-based Markov Model	Provider	50-year	T2DM. Not being treated with diabetic medications and without autoimmune diabetes
United Kingdom	Ren *et al*., 2023[10]	Metformin (Binguanid), SGLT-2i	IQVIA Core Diabetes Model (V.9.0)	Provider	50-year	Type 2 diabetes with inadequate glycaemic control on metformin plus an SGLT-2 inhibitor
Denmark	Pulleybank *et al*., 2023[11]	Empaglifozin (SGLT-2i), sitagliptin (DPP-4i)	A Markov-type cohort model	Payer	40-year	Patients with age 55 - 57 years old, between 6.6 – 8.6 years of historical diabetes diagnosis, and baseline HbA1c levels 8.1-8.3
China	Feng *et al*., 2023[12]	Placebo, injectable GLP-1	The United Kingdom Prospective Diabetes Study Outcome Model version 2.1	Payer	40-year	1,000 subjects in each intervention group, with a mean age of 61, a mean HbA1c of 8.2%+0.7%.

Country	First author, year	Comparison (Oral Semaglutide vs Treatment B)	Model	Perspective	Time Horizon	Participants (disease condition and/or medications)
United Kingdom	Risebrough *et al*., 2021[13]	Dulaglutide (GLP-1), Liraglutide (GLP-1)	Hypothetical cohort	Payer	50-year	Adults with T2D with inadequate HbA1c control with 1 to 2 OADs.
United Kingdom	Bain *et al*., 2021[14]	Empagliflozin (SGLT-2i), Sitagliptin (DPP-4i), Liraglutide (GLP-1)	IQVIA Core Diabetes Model (V.9.0)	Payer	50-year	Type 2 diabetes with HbA1c values 7.5-10% who receiving metformin with or without a sulfonylurea or SGLT2i.
United States of America	Cui *et al*., 2021[15]	Empagliflozin (SGLT-2i), Sitagliptin (DPP-4i), Liraglutide (GLP-1)	Decision tree analysis model	Payer	52-week	Type 2 diabetes who are resistant to or not candidates for injectable therapies.
Denmark	Ehlers *et al*., 2022[(16)]	Empagliflozin (SGLT-2i)	IQVIA Core Diabetes Model (V.9.5)	Danish health sector (provider)	50-year	For patients with a mean age was 58 years, the mean duration of diabetes was 7.4 years, and the mean HbA1c was 8.1%.
Swedish	Eliasson *et al*.,2022[17]	Empagliflozin (SGLT-2i), Sitagliptin (DPP-4i)	Validated Institute for Health Economics Diabetes Cohort Model (IHE-DCM)	Payer and Societal	40-year	HbA1c reached a level of 8.0%, at which point basal insulin was started, and existing study treatment was discontinued.

Country	First author, year	Comparison (Oral Semaglutide vs Treatment B)	Model	Perspective	Time Horizon	Participants (disease condition and/or medications)
United States of America	Guzauskas *et al*., 2021[18]	Empagliflozin (SGLT-2i), Liraglutide (GLP-1), Sitagliptin (DPP-4i), Background therapy	The model was developed in Microsoft Excel for Office 365, version 1911.	Provider	50-year	Adults with inadequate glycaemic control despite being currently treated with antihyperglycemic agents.

Explanation: T2DM: Type 2 Diabetes Mellitus; OAD: Oral Antidiabetic Drug; SGLT-2i: Sodium-Glucose Co-Transporter 2 Inhibitor; DPP-4i: Dipeptidyl Peptidase 4 Inhibitor; GLP-1: Glucose Like Peptide 1 Receptor Agonist; HbA1c: Hemoglobin A1c.

Table 2. The Economic Outcomes of Included Studies with Oral Semaglutide Intervention

Country	First Author, Year	Comparator	ICER Values	WTP Threshold (Cost/QALY)	CE Conclusion	Decision
Portugal	Malkin *et al.,* 2022[7]	Empaglifozin	EUR23,571/QALY	EUR30,000/QALY	Cost-effective	Yes
		Dulaglutide	EUR23,297/QALY			
Netherlands	Malkin *et al*., 2021[8]	Empaglifozin	EUR13,770/QALY	EUR20,000/QALY	Cost-effective	Yes
		Sitagliptin	EUR5,938/QALY			
		Liraglutide	Oral Semaglutide dominant		Cost savings	
USA	Choi *et al*., 2022[9]	SGLT2i	USD1,024,000/QALY	USD150,000/QALY	Requiring cost reduction of at least 70%	No
		Metformin	USD300,000/QALY		Requiring cost reduction of at least 90%	
UK	Ren *et al*., 2023[10]	Metformin+SGLT2i	GBP 9,404/QALY	GBP20,000/QALY	Cost-effective	Yes
Denmark		Empaglifozin	EUR20,189/QALY	EUR50,000/QALY	Cost-effective	Yes

Country	First Author, Year	Comparator	ICER Values	WTP Threshold (Cost/QALY)	CE Conclusion	Decision
	Pulleybank *et al*., 2023[11]	Sitagliptin	EUR12,746/QALY			
China	Feng *et al*., 2023[12]	Dulaglutide	USD34,061.37/QALY	USD36,528.3/QALY	Cost-effective	Yes
		Liraglutide	USD33,041.06/QALY			
		Lixisenatide	USD21,668.64/QALY			
		Exenatide	USD88,776.61/QALY		Requiring cost reduction of at least 8.6%	No
		Placebo	USD39,853.22/QALY			
UK	Risebrough *et al*., 2021[13]	Duraglutide	Oral Semaglutide dominant	USD150,000/QALY	Cost savings	Yes
		Liraglutide	Oral Semaglutide dominant			
UK	Bain *et al*., 2021[14]	Empagliflozin	GBP11,006/QALY	GBP20,000/QALY	Cost-effective	Yes
		Sitagliptin	GBP4,930/QALY			
		Liraglutide	Oral Semaglutide dominant		Cost savings	
USA	Cui *et al*., 2021[15]	Empagliflozin	USD6,650/1%HbA1c reduction	NA	There can't be a conclusion because there was no WTP-Threshold	No conclusion
		Sitagliptin	USD6,207/1%HbA1c reduction			
		Liraglutide	Oral Semaglutide dominant		Cost savings	Yes
Denmark	Ehlers *et al*., 2022(16)	Empagliflozin	DKK1,930,548/QALY	DKK357,100/QALY	Requiring cost reducing	No
Swedish	Eliasson *et al*.,2022[17]	**Payer Perspective**		SEK500,000/QALY	**Payer Perspective**	
		Empagliflozin	SEK239,001/QALY		Cost-effective	Yes
		Sitagliptin	SEK120,848/QALY			
		Societal Perspective			**Societal Perspective**	
		Empagliflozin	SEK191,721/QALY		Cost-effective	Yes
		Sitagliptin	SEK95,234/QALY			
USA		Empagliflozin	USD458,400/QALY	USD150,000/QALY	Not cost-effective	No

Country	First Author, Year	Comparator	ICER Values	WTP Threshold (Cost/QALY)	CE Conclusion	Decision
	Guzauskas *et al*., 2021[18]	Liraglutide	USD40,100/QALY		Cost-effective	Yes
		Sitagliptin	USD145,200/QALY			
		Background Therapy	USD117,500/QALY			

Explanation: NA: Not Available; WTP: Willingness-To-Pay; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Years; USA: United States of America; UK: United Kingdom; SGLT2i: Sodium-Glucose Co-Transporter 2 inhibitor; EUR: Euro; USD: United State Dollar; GBP: British Poundsterling; DKK: Danish Crone; SEK: Swedish Krona; Yes: cost-effective; No: no cost-effective; No Conclusion: cannot determined.

Table 3. Quality Assessment Result

First Author, Year	Malkin *et al.*, 2022[7]	Malkin *et al*., 2021[8]	Choi *et al*., 2022[9]	Ren *et al*., 2023[10]	Pulleybank *et al*., 2023[11]	Feng *et al*., 2023[12]	Risebrough *et al*., 2021[13]	Bain *et al*., 2021[14]	Cui *et al*., 2021[15]	Ehlers *et al*., 2022[(16)]	Eliasson *et al*., 2022[17]	Guzauskas *et al*., 2021[18]
Title	1	1	1	1	1	1	1	1	1	1	1	1
Abstract	1	1	1	1	1	1	1	1	1	1	1	1
Background and objective	1	1	1	1	1	1	1	1	1	1	1	1
Health economic analysis plan	1	1	1	1	1	1	1	1	1	1	1	1
Study population	1	1	1	1	1	1	1	1	1	1	1	1
Setting and location	1	1	1	1	1	1	1	1	1	1	1	1
Comparators	1	1	1	1	1	1	1	1	1	1	1	1
Perspective	1	1	1	1	1	1	1	1	1	1	1	1
Time horizon	1	1	1	1	1	1	1	1	1	1	1	1
Discount rate	1	1	1	1	1	1	1	1	0	1	1	1
Selection of outcomes	1	1	1	1	1	1	1	1	1	1	1	1
Measurement of outcomes	1	1	1	1	1	1	1	1	1	1	1	1

First Author, Year	Malkin *et al.*, 2022[7]	Malkin *et al.*, 2021[8]	Choi *et al.*, 2022[9]	Ren *et al.*, 2023[10]	Pulleybank *et al.*, 2023[11]	Feng *et al.*, 2023[12]	Risebrough *et al.*, 2021[13]	Bain *et al.*, 2021[14]	Cui *et al.*, 2021[15]	Ehlers *et al.*, 2022[16]	Eliasson *et al.*, 2022[17]	Guzauskas *et al.*, 2021[18]
Valuation of outcomes	1	1	1	1	1	1	1	1	1	1	1	1
Measurement and valuation of resources and cost	1	1	1	1	1	1	1	1	1	1	1	1
Currency, price date, and conversion	1	1	1	1	1	1	1	1	0	1	1	1
Rationale and description of model	1	1	1	1	1	1	1	1	1	1	1	1
Analytics and assumptions	1	1	1	1	1	1	1	1	1	1	1	1
Characterizing heterogeneity	1	1	1	1	1	1	1	1	1	1	1	1
Characterizing distributional effects	1	1	1	1	1	1	1	1	1	1	1	1
Characterizing uncertainty	1	1	1	1	1	1	1	1	1	1	1	1
Approach to engagement with patients and others affected by the study	1	1	1	1	1	1	1	1	1	1	1	1
Study parameter	1	1	1	1	1	0	1	1	0	0	1	0
Summary of main results	1	1	0	1	1	1	1	1	0	1	1	1
Effect of uncertainty	1	1	1	1	1	1	1	1	1	1	1	1
Effect of engagement with patients and others affected by the study	1	1	0	1	1	1	1	1	1	1	1	1
Study results, limitations, generalizability, and current knowledge	1	1	1	1	1	1	1	1	1	1	1	1
Source of funding	1	1	1	1	1	1	1	1	1	1	1	1
Conflicts of interest	1	1	1	1	1	1	1	1	1	1	1	1
Total Score	28	28	26	28	28	27	28	28	24	27	28	27
Percentage (%)	100	100	92,86	100	100	96,43	100	100	85,71	96,43	100	96,43

Explanation: Quality assessment; High Quality (> 75%); Moderate Quality (50% to 75%); Poor Quality (<50%).

DISCUSSION

Oral GLP-1 represents a generation of antidiabetic drugs that have been developed to enhance patient preference, compliance, and convenience.[19] For instance, Semaglutide was designed for oral administration and has been singled out in the American Diabetes Association/The European Association for The Study of Diabetes (ADA/EASD) consensus report for its "very high" efficacy in lowering blood glucose and controlling body weight among individuals with T2DM. It is recognized as the first GLP-1 developed for oral administration.[20,21] However, the high cost, which is characteristic of new-generation drugs, may present a barrier to routine use, necessitating an evaluation of cost-effectiveness. As anticipated, the systematic review showed that the use of oral Semaglutide at various doses appeared to be cost-effective, but this is contingent upon careful consideration of the comparators. In the majority of cases, oral Semaglutide proved to be cost-effective compared to other SGLT-2 and subcutaneous GLP-1 receptor agonists. Compared to the standard of care, it was not cost-effective due to its higher cost. For instance, as shown by Choi, *et al*., oral Semaglutide, when compared to standard care of lifestyle intervention and metformin, was deemed cost-effective at under USD150,000/QALY, while the current ICER was USD327,000/QALY.[9] Conversely, two studies reported that oral Semaglutide was not cost-effective compared to empagliflozin. These studies reported that cost was too high and the differences in QALYs gained were not significant.[16,18]

Based on efficacy and safety, oral Semaglutide at doses of 7 mg or 14 mg has been reported to significantly reduce HbA1c by 0.26% or 0.38%, respectively. Other doses have shown significant reductions in body weight, offering benefits in terms of glycemic control, as well as cardiovascular and renal health.[4,20,22] Treatment with the drug may represent an effective and safe option for individuals with T2DM who intend to lower glucose levels and reduce body weight. The QALYs gained from using oral Semaglutide were consistently found to be higher than those of the comparators. However, two out of 12 studies found no significant differences in QALY values compared to the comparators.

Oral Semaglutide is associated with a higher cost compared to other antidiabetic medications including SGLT2 and DPP4 inhibitors, as well as other conventional therapies namely Biguanides and Sulfonylureas. However, compared to injectable GLP-1, its price is lower. Risebourgh *et al* reported that oral Semaglutide increased cost savings and was a more effective treatment for T2DM patients who were inadequately controlled with one to two oral antidiabetic medications. This pattern suggests that cost considerations and the monetary value a system is willing to pay primarily drive uncertainties in cost-effectiveness.

Based on the results, the most significant sources of uncertainty in ICER values include differences in time horizon (*n*=5), discount rate (*n*=3), treatment cost (*n*=3), and treatment policy estimand (*n*=1). Standard CEA practice guidelines recommend using a time horizon that adequately captures cost and outcomes to ensure more accurate results. Failure to adhere to these guidelines may lead to an incomplete representation of intervention impacts.[23] Inflation of drug cost over time can lead to changes in conclusion regarding cost-effectiveness compared to the alternatives.

Major evidence supporting the cost-saving benefits of using oral Semaglutide was obtained from high-income countries, including the United States of America and the United Kingdom (n=3, each). These results show that studies on the development of oral Semaglutide have primarily been conducted in high-income countries, possibly due to the elevated

product cost and the need for improved technology to ensure sufficient bioavailability.[24] The high cost may limit accessibility in lower-income countries, where investigations and development may be less feasible. From a broader perspective, all viewpoints can provide insights into these results. The societal perspective is often considered the gold standard in pharmacoeconomic studies because it offers the advantage of incorporating various factors into economic evaluation. This approach may lead to more optimal resource allocation in decision-making processes and also supports informed public discussions regarding healthcare policies and interventions.[25]

Other systematic reviews found that certain antidiabetic medications are more cost-effective compared to others. For instance, Yoshida *et al* conducted an analysis on the cost-effectiveness of Sodium-Glucose Cotransporter Inhibitors for T2DM. It was found that SGLT2 inhibitors, whether used as mono, dual, or triple therapy were cost-effective compared to SoC/metformin or other antidiabetic therapies, including DPP-4 inhibitors, Sulfonylurea, Thiazolidinediones (TZD), Alpha Glucosidase Inhibitors (AGI), or insulin. However, compared to injectable GLP-1, SGLT2 inhibitors were not found to be cost-effective.[26] Yang *et al.* stated that GLP-1 receptor agonists were found to be cost-effective compared to insulin therapy.[27] It was also deemed cost-effective in subgroup analyses in the short term rather than the long term.[28] These results show that GLP-1 receptor agonists are cost-effective when compared to other antidiabetic medications.

This review has several limitations, firstly, only English-language journals were included, which may have led to missing relevant studies published in other languages. Secondly, there was variability in cost values derived from different countries. The ideal approach would have been to standardize cost values, for instance, by using the US dollar as a common currency. Thirdly, all studies were conducted in high-income countries, presumably due to the tendency of governments in high-income countries to prioritize cost-effectiveness evidence in their healthcare system.

RECOMMENDATION

In conclusion, the advancement of oral GLP-1 represents a significant breakthrough in antidiabetic medications. This systematic review shows that oral Semaglutide is cost-effective compared to other antidiabetic medications. The drug has great potential as a cost-effective treatment option for T2DM. CEAs should improve the methods to support subsequent implementation and reimbursement decisions. Future studies are recommended to include the RCT design in assessing the cost-effectiveness of oral Semaglutide for T2DM treatment and explicitly report all analytic inputs (values, ranges, references), including uncertainty or distributional assumptions.

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