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REVIEW

Health Technology Assessment: Evaluation of 7 Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus

Zeyu Xie, Jia Hu, Mengting Li, Xiao Hu, Jisheng Chen

Key Specialty of Clinical Pharmacy, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, People's Republic of China

Correspondence: Jisheng Chen, Key Specialty of Clinical Pharmacy, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, 510080, People's Republic of China, Tel +86 20-87622305, Fax +86 20-61321967, Email cjslym@163.com

Purpose: This study provides a reference for healthcare organizations in the selection and rational use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), based on the Rapid Guide for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition).

Methods: According to the Rapid Guide for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition) released in 2023, relevant databases such as PubMed, Cochrane, and Embase, drug labels, and clinical guidelines were searched for drug information. We systematically evaluated 7 GLP-1RAs marketed in China for safety, efficacy, economy, pharmacological properties, and other attributes using a percentage scoring method.

Results: The final assessment result scores from highest to lowest were semaglutide (71.5 points), dulaglutide (68.9 points), liraglutide (68.7 points), exenatide (62.5 points), lixisenatide (59.9 points), polyethylene glycol loxenatide (55.9 points), and benaglutide (45.1 points).

Conclusion: When a healthcare organization introduces GLP-1RAs to their hospital, they can refer to the assessment results and use the top three recommended medications: semaglutide, dulaglutide, and liraglutide.

Keywords: glucagon-like peptide-1 receptor agonist, health technology assessment, type 2 diabetes mellitus, drug evaluation

Introduction

Hospital-based health technology assessment (HB-HTA) refers to the comprehensive and systematic evaluation of relevant health technologies based on the actual needs of hospitals, using the principles and methods of evidence-based medicine and health technology assessment to make rapid decisions about the selection, acquisition, and use of new technologies to improve health equity and is a commonly used policy analysis tool internationally.[1,2]

The incidence of diabetes is increasing due to changes in diet and lifestyle. Type 2 diabetes mellitus (T2DM) accounts for approximately 98% of diabetes diagnoses globally, although the exact proportion varies greatly from country to country.[3] It is estimated that 530 million adults worldwide have diabetes, with a global prevalence of 10.5% among adults aged 20–79 years.[4,5] The prevalence of diabetes among adults aged 20–79 years in China increased by 71.1%, from 4.7% in 1990 to 8.0% in 2019. Furthermore, the prevalence of diabetes among adults aged 20–79 in China is projected to increase from 8.2% to 9.7% in 2020–2030 compared with 2019. These statistics highlight the severity of the T2DM epidemic in China.

According to a 2016 report, over 1.9 billion adults aged 18 or older were overweight worldwide, with more than 650 million being obese. The report also found that 39% of adults aged 18 or older were overweight and 13% were obese.[6] Overweight and obesity are significant risk factors for developing T2DM.[7] Patients with T2DM are frequently overweight or obese, and obesity exacerbates the risk of cardiovascular disease in these patients. Weight reduction can help delay the progression of prediabetes to T2DM. Furthermore, Diabetes is a risk factor

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for cardiovascular disease, which is the leading cause of death in patients with diabetes.[8] Patients with diabetes have a 2–4 times higher risk of cardiovascular disease compared to those without diabetes.[9] Most patients diagnosed with T2DM are between 50 and 60 years old and are at a high risk for atherosclerotic cardiovascular disease (ASCVD) if they are aged 40 or older.

GLP-1RAs is currently widely used in clinical practice due to its significant benefits. It has been shown to reduce body weight, reduce the risk of ASCVD, and improve atherosclerosis and lipids, in addition to its significant glucose-lowering effects. The 2023 American Diabetes Association guidelines recommend GLP-1RAs or sodium-glucose cotransporter-2 inhibitors (SGLT-2i) with cardiovascular benefits as one of the indispensable medications for the treatment of T2DM, along with significant weight loss, in addition to metformin therapy.[10] There are several drugs available for treating T2DM, including 7 GLP-1RAs injections that have been marketed in China to date. Additionally, an oral form of GLP-1RAs, as well as a GIP and GLP-1 dual agonist (tirzepatide), will also be marketed in China. This may pose challenges for healthcare organizations screening GLP-1RAs for introduction into their hospitals, particularly for those without the capacity to conduct drug evaluations independently. Therefore, given the wide range of GLP-1RAs currently available on the market, scientific evaluation and drug selection can ensure that healthcare organizations introduce advantageous drugs in a timely manner. This is conducive to guaranteeing that patients receive safe, effective, economical, and appropriate drug therapy. The objective of this study was to assess 7 GLP-1RAs that marketed in China based on the "2023 Rapid Guidelines for Drug Evaluation and Selection in Chinese Healthcare Organizations (Second Edition)",[11] so as to provide a reference for healthcare organizations in introducing and rationalizing the use of GLP-1RAs.

Methods

Evaluation Basis

Based on the "Rapid Guidelines for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition)" published in 2023,[11] and applying a percentage assessment model to evaluate 7 GLP-1RAs. In terms of pharmacological properties, the main evaluation of the drug's pharmacological effects, in vivo processes, whether the pharmacology and methods of use are clear, the length of the drug's expiration date and storage requirements. In terms of drug effectiveness, the main evaluation is the clinical effectiveness of the drug, the recommendation level of relevant authoritative professional information such as clinical guidelines or expert consensus. Regarding safety, the evaluation mainly focuses on adverse events, drug use in special populations, and drug interactions. In terms of economics, the drug's average daily therapeutic cost is being evaluated. Information on the availability of drugs is evaluated.

Data Source

Drug labels, drug registration information, some government websites (eg, American Food and Drug Administration (FDA), National Medical Products Administration (NMPA) provide safety information. English databases PubMed, Embase, and Cochrane Library, as well as Chinese databases Chinese Biomedical Sciences (CBM) and China National Knowledge Infrastructure (CNKI), were searched for systematic evaluations, meta-analyses, and real-world studies on the safety and efficacy of GLP-1RAs in treating T2DM. High-quality guidelines for the treatment of type 2 diabetes issued by an authoritative organization within 5 years (eg, American Diabetes Association). Search terms: semaglutide, liraglutide, PEX 168, exenatide, lixisenatide, dulaglutide, benaglutide, glucagon-like peptide-1 receptor agonist.

Evaluated Drug and Contents

The 7 GLP-1RAs marketed in China are exenatide injection, liraglutide injection, lixisenatide injection, benaglutide injection, dulaglutide injection, polyethylene glycol (PEG) loxenatide injection, and semaglutide injection. The evaluation of the 7 GLP-1RAs included an assessment of their pharmacologic properties (28%), efficacy (27%), safety (25%), economy (10%), and other attributes (10%). Table 1 displays the basic information on the 7 GLP-1RAs marketed in China.

Table 1 The 7 GLP-1RA Basic Information

Common Name	Approved Regions (Year)
Exenatide Injection,	China (2009), Europe (2010), United States (2005), Japan (2010)
Liraglutide Injection	China (2011), Europe (2009), United States (2010), Japan (2010)
Lixisenatide Injection	China (2018), Europe (2013), United States (2016), Japan (2013)
Benaglutide Injection	China (2016)
Dulaglutide Injection	China (2019), Europe (2014), United States (2014), Japan (2015)
Polyethylene Glycol Loxenatide Injection	China (2019)
Semaglutide Injection	China (2021), Europe (2018), United States (2017), Japan (2018)

Analysis and Evaluation

Drugs included in the evaluation were assigned a score according to the drug evaluation guidelines based on evidence collected by searching relevant databases.[11] If no scoring breakdown rules exist, experts in the field are invited to refine them. The evaluation was conducted by two clinical pharmacists independently. In case of conflicting results, experts in the relevant fields were invited to discuss the evaluation results. The evaluation results will eventually be used to select medicines for medical institutions and make decisions about clinical medication programs.

Results

Pharmacological Properties (28%)

Pharmacological Effects and in vivo Processes

7 GLP-1RAs with obvious clinical efficacy, clear and innovative mechanism of action, all scoring 5 points; at the same time, the in vivo process, pharmacokinetic parameters are complete, scoring 5 points.

Pharmacy and the Use of Drugs

The ingredients and excipients of the 7 GLP-1RAs are clearly defined; the dosage forms are all subcutaneous/intramuscular injections, and to avoid serious gastrointestinal adverse events, it is necessary to start with a low dosage and gradually increase the dosage during use. In terms of specifications and packaging, all 7 GLP-1RAs are compatible with clinical use and dosage can be adjusted. In terms of administration frequency, exenatide was given twice daily, benaglutide three times daily, liraglutide and lixisenatide once daily, and dulaglutide, PEG loxenatide, and semaglutide once weekly. In addition, in terms of ease of use, all patients treated with GLP-1RAs need to be trained by a healthcare provider.

Drug Storage Conditions and Expiration Dates

All 7 GLP-1RAs must be refrigerated for storage. Exenatide, lixisenatide, and semaglutide have an expiration date of 36 months, while liraglutide has an expiration date of 30 months. PEG loxenatide, benaglutide, and dulaglutide have an expiration date of 24 months. Table 2 displays the results of the pharmacologic properties evaluations for the 7 GLP-1RAs.

Efficacy (27%)

Indications

The approved indications for all 7 GLP-1RAs in China are for glycemic control in adult patients with T2DM. Based on the Chinese Lipid Management Guidelines 2023,[12] patients who are diagnosed with T2DM and are aged 40 years or older can be considered a high-risk group for ASCVD. Liraglutide, dulaglutide, and semaglutide have been shown to reduce the risk of major cardiovascular in adult patients with T2DM and are clinically indicated/sub selected, scoring 3 points. Exenatide, lixisenatide, benaglutide, and PEG loxenatide scored 1 point for having a neutral profile of major cardiovascular benefit or for having no studies, and being the clinically More drugs available.

Guideline Recommendations

Guidelines and expert consensus on the clinical use of GLP-1RAs suggest that GLP-1RAs reduce cardiovascular risk in T2DM (eg, 2020 Chinese Guidelines for the Prevention and Control of Type 2 Diabetes Mellitus, 2022 Chinese Clinical

Table 2 Pharmacological Properties Score Results

Pharmacological Properties (28point)		Grade	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
Pharmacological effect (5 point)	Clinical efficacy obvious, action mechanism is clear, mechanism or target is innovative	5	5	5	5	5	5	5	5
	Clinical efficacy obvious, mechanism is clear	4							
	Clinical efficacy general, mechanism is unclear	2							
	Clinical efficacy poor, mechanism is unclear	1							
In vivo processes (5 points)	In vivo process clear, pharmacokinetic parameters complete	5	5	5	5	5	5	5	5
	In vivo process clear, pharmacokinetic parameters not complete	3							
	In vivo process not clear, pharmacokinetic parameters not complete	1							
Pharmacy and the use of drugs (12 point)	Main ingredients and excipients	2	2	2	2	2	2	2	2
	Specification and Packaging	2	2	2	2	2	2	2	2
	Dosage form (oral/inhalation/topical preparations (2 pts), subcutaneous/intramuscular injections (1.5 pts), intravenous drip/injection (1 pt))	2	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Dose of administered (fixed dosage (2 pts), dosage adjustment required during use (1.5 pts), dosage based on body mass or body surface area (1 pt))	2	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Administration frequency (1x/weeks, (2 pts); 1x/d (1 point); ≥2x/d (0.5 pts)	2	0.5	1	1	1	2	2	2
	Convenient use (self-administered without assistance (2 pts), self-administered without assistance, with help or training (1.5 pts), administered by medical personnel (1 pt))	2	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Storage conditions (4 points)	Room temperature storage	3							
	Cool storage	2							
	Refrigerated/frozen storage	1	1	1	1	1	1	1	1
	No need for shading/sheltering	1							
Expiration dates (2 point)	>60 months	2							
	≥36 months, <60 months	1.5	1.5		1.5				1.5
	≥24 months, <36 months	1		1		1	1	1	
	≥12 person-months, <24 months	0.5							
	<12 months	0.25							
The results of the pharmacological properties		28	21.5	21.5	22	20.5	22.5	22.5	23

Guidelines for the Prevention and Control of Type 2 Diabetes Mellitus in the Elderly, and 2023 American Diabetes Association Standards for the Medical Diagnosis and Treatment of Diabetes Mellitus). The recommendations of the guidelines and expert consensus are shown in Table 3.

Table 3 recommends liraglutide, dulaglutide, and semaglutide for the treatment of T2DM combined with CVD, with a grade of recommendation of I A and a score of 12. Exenatide and lixisenatide are mentioned as neutral for CVD in guidelines and expert consensus, with neutral results from the cardiovascular outcomes (CVOT) study. In the 2019 ESC/EASD Guidelines, lixisenatide and exenatide are mentioned as neutral in terms of their effect on the risk of hospitalization for HF and may be considered for the treatment of T2DM combined with HF, with a grade of recommendation of IIb. Benaglutide and PEG loxenatide are no guideline or expert consensus recommendations and lack of data from the CVOT study, both scored 6 points.

Table 3 Recommendations in Domestic and Foreign Guides and Consensus

Guide Name	Guideline Makers and Sources	Recommended Medications	Recommended Content	Evidence level
2020 Guidelines for the prevention and treatment of type 2 diabetes in China[13]	Diabetes Branch of Chinese Medical Association	GLP-1RA with evidence of ASCVD benefit	GLP-1RA or SGLT2i with evidence of ASCVD benefit should be added to metformin in patients with type 2 diabetes with ASCVD or high cardiovascular risk, regardless of whether their HbA1c is up to standard or not, as long as there are no contraindications	A
Standards of Medical Care in Diabetes—2023[10]	American Diabetes Association	GLP-1RA with evidence of ASCVD benefit	SGLT2i or GLP-1 RAs with cardiovascular benefits are recommended as glucose-lowering therapy in T2DM patients with ASCVD or ASCVD high-risk factors, renal disease, or heart failure, regardless of baseline HbA1c levels.	A
Clinical Guidelines for Prevention and Treatment of Type 2 Diabetes in the Elderly in China (2022 Edition)[14]	Chinese Geriatrics Society Geriatric Endocrinology and Metabolism Branch, China Geriatric Health Medical Research Association	GLP-1RA with evidence of ASCVD benefit	In type 2 diabetes complicated with ASCVD or high-risk factors, CKD or HF, GLP-1RA is preferred according to individual patient conditions.	I A
Italian guidelines for the treatment of type 2 diabetes (2022)[15]	Italian Society of Diabetology, Italian Association of Medical Diabetologists	GLP-1RA	We recommend using metformin, SGLT-2 inhibitors or GLP-1 receptor agonists as first-line long-term treatment in patients with type 2 diabetes with previous cardiovascular events and without heart failure.	Strong Moderate
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD[16]	European Society of Cardiology, European Association for the Study of Diabetes	Lixisenatide, Exenatide GLP-1RA with evidence of ASCVD benefit	1. Lixisenatide, liraglutide, semaglutide, exenatide and dulaglutide have a neutral effect on the risk of HF hospitalization and can be considered for the treatment of HF patients with diabetes 2. GLP-1RAs Liraglutide, semaglutide, or dulaglutide is recommended to reduce cardiovascular events in T2D patients with CVD or at very high/high cardiovascular risk	II b A I A
CLINICAL PRACTICE GUIDELINES: MANAGEMENT OF TYPE 2 DIABETES MELLITUS (6th Edition)[17]	Ministry of Health Malaysia	Liraglutide, Dulaglutide, Semaglutide	In patients with type 2 diabetes with atherosclerotic cardiovascular disease, ASCVD or high risk, renal disease, or markers of heart failure, SGLT-2 inhibitors or GLP-1 RAs are recommended.	A
2020 Guidelines on the management of diabetic patients. A position of Diabetes Poland[18]	Polskie Towarzystwo Diabetologiczne	GLP-1RA with evidence of ASCVD benefit	GLP-1RAs with established beneficial effects on cardiovascular risk should be considered first in patients with cardiovascular disease, especially before myocardial infarction	A
Clinical expert consensus on glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of type 2 diabetes [5]	Endocrinology Branch of Chinese Medical Association, Chinese Journal of Internal Medicine	Liraglutide, Dulaglutide, Semaglutide	1. It is recommended for type 2 diabetes patients with ASCVD or very high cardiovascular risk, which can reduce the risk of cardiovascular events.	/

(*Continued*)

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Table 3 (Continued).

Guide Name	Guideline Makers and Sources	Recommended Medications	Recommended Content	Evidence level
2020 American College of Cardiology "Expert consensus decision pathway for novel therapies to reduce cardiovascular risk in patients with type 2 diabetes mellitus"[19]	American College of Cardiology	GLP-1RA with evidence of ASCVD benefit	Patients with T2DM with one or more ASCVD or high risk of ASCVD may choose GLP-1RA therapy with cardiovascular benefits.	/
Consensus Recommendations by the Asian Pacific Society of Cardiology: Optimizing Cardiovascular Outcomes in Patients with Type 2 Diabetes[20]	Asia-Pacific Society of Cardiology	GLP-1RA with evidence of ASCVD benefit	In patients with T2DM with normal renal function and high risk of cardiovascular events, GLP-1RA with proven cardiovascular benefit is recommended.	/
Expert consensus on the diagnosis and treatment of cardiovascular disease in patients with diabetes mellitus n[21]	National Health Commission Capacity Building and Continuing Education Center	GLP-1RA with evidence of ASCVD benefit	In patients with ASCVD, the preferred GLP-1RA with proven cardiovascular benefit should be considered for glycemic and weight control.	/

Abbreviations: chronic kidney disease: CKD; atherosclerotic cardiovascular disease: ASCVD; sodium-dependent glucose transporters 2 inhibitors: SGLT2i; type 2 diabetes mellitus: T2DM.

Clinical Efficacy

The primary endpoint efficacy indicator was HbA1c (6 points). Secondary efficacy endpoints included weight loss (2 points) and risk of cardiovascular benefit (2 points). The class of drugs' highest indicator of improved efficacy is considered to have a perfect score.

The results of the basic information on HbA1c reduction, weight loss, and cardiovascular benefits of the 7 GLP-1RAs are shown in Table 4. The study was conducted by searching PubMed and Cochrane Library Medical Database. The meta-analysis study by Tsapas, Apostolos et al[22] evaluated the HbA1c lowering effects of different glucose-lowering agents, including 5 GLP-1RAs, through 453 trials that assessed nine antidiabetic interventions from 21 drug classes. Shi-Shen et al[23] conducted a meta-analysis of polyethylene glycol loxenatide, which included the percentage of HbA1c reduction and weight loss. Xia, Lin et al[24] also conducted a meta-analysis, which included 36 RCTs with a total of 11,126 patients comparing the effect of 8 GLP-1RAs on weight loss in patients with T2DM. Additionally, the drug label did not provide any study data on weight loss for benaglutide. Similarly, there was no significant difference in weight loss between PEG loxenatide and placebo. Furthermore, there were no study data available on CVOT for either benaglutide or PEG loxenatide.

The results of HbA1c reduction, weight loss, and cardiovascular benefits of the 7 GLP-1 RAs are shown in Table 4, it can be seen that semaglutide reduced HbA1c the most (−1.33%) among 7 GLP-1 RAs, scoring 6 points. Dulaglutide, PEG loxenatide, and liraglutide lowered HbA1C in essentially similar and all scored 4 points. In the term of weight loss and cardiovascular benefit, semaglutide also had a significant weight reduction advantage (−4.27 kg) and a cardiovascular benefit, scoring 4 points.

Overall, on the primary outcome endpoint (HbA1c), exenatide, liraglutide, lixisenatide, benaglutide, dulaglutide, PEG loxenatide, and semaglutide scored 3, 4, 2, 1, 4, 4, and 6, respectively. At the secondary outcome endpoint (weight loss + cardiovascular benefit), the scores for exenatide, liraglutide, lixisenatide, benaglutide, dulaglutide, PEG loxenatide, and semaglutide were 2, 3, 1.5, 0, 2.5, 0, and 4, respectively. The efficacy scores result of the 7 GLP-1RAs are shown in Table 5.

Safety

Adverse Events

The most common adverse events of the 7 GLP-1RAs were gastrointestinal reactions, which were mild to moderate, with an incidence of >10%, all of which were scored as 1 point. Mild to moderate adverse events (eg, hypoglycemia, gastrointestinal, injection site reactions, etc.) were noted for both benaglutide and PEG Loxenatide. In addition, the incidence of serious adverse events ranged from 0.01% to <0.1%, scoring 4 points. The incidence of serious adverse events (eg, necrotizing or hemorrhagic pancreatitis, acute kidney damage and renal failure, anaphylactic reactions, and hypoglycemic aspects) for exenatide, liraglutide, and dulaglutide ranged from 0.01% to <0.1%, scoring 4 points. The

Table 4 The Results of HbA1c Reduction, Weight Loss, and Cardiovascular Benefits of the 7 GLP-1 RAs

Drug	HbA1c%	Weight loss (kg)	Cardiovascular Benefits	
			ASCVD	HF
Exenatide	−0.60 (−0.73 to −0.47) [a]	1.53kg (0.75 to 2.31) [c]	Neuter	Neuter
Liraglutide	−0.80 (−0.89 to −0.70) [a]	1.85kg (1.34 to 2.36) [c]	Benefit	
Lixisenatide	–0.43 (–0.57 to –0.29) [a]	0.76kg (0.11 to 1.41) [c]	Neuter	
Benaglutide	−0.26[d]	NA	NA	
Dulaglutide	−0.89 (−1.05 to −0.73) [a]	1.10kg (0.54 to 1.66) [c]	Benefit	
PEG Loxenatide	−0.95 (−1.09, −0.81) [b]	NA	NA	
Semaglutide	−1.33 (−1.50 to −1.16) [a]	4.27kg (3.53 to 5.01) [c]	Benefit	

Note: HF: heart failure; ASCVD: Atherosclerotic cardiovascular disease; [a] Data from Tsapas, Apostolos et al (2020);[22] [b]Data from Chen Shiet al (2021);[23] [c]Data from Xia, Lin et al (2021);[24] [d]Data from drug label. NA: no data or not significant different.

Table 5 Efficacy Score Results

Efficacy (27%)		Grade	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
Indications (5 points)	Clinically necessary and preferred	5							
	Clinical need, second choice	3		3			3		3
	More drugs available	1	1		1	1		1	
Guideline recommendations (12 points)	Diagnostic and treatment protocols/clinical pathways, consensus/management approaches issued by national health administrative agencies, etc., and guideline Level I recommendations (12 points for Level A evidence, 11 points for Level B evidence, and 10 points for Level C evidence and others).	12		12			12		12
	Guideline Level II and below recommendations (9 points for Level A evidence, 8 points for Level B evidence, and 7 points for Level C evidence and others).	9	9		9				
	Expert Consensus Recommendations (6 points for consensus issued by a Society organization based on systematic evaluation, 5 points for consensus issued by a Society organization, and 4 points for others).	6				6		6	
	Systematic Evaluation/Meta-Analysis (3 points for large sample, high quality systematic evaluation/meta-analysis, 2 points for small sample, low quality systematic evaluation/meta-analysis, and 1 point for systematic evaluation/meta-analysis of non-RCT studies).	3							
Clinical efficacy (10 points)	Primary efficacy endpoints	6	3	4	2	1	4	4	6
	Secondary efficacy endpoints	4	2	3	1.5	0	2.5	0	4
The results of the efficacy		27	15	22	13.5	8	21.5	11	25

incidence of serious adverse events (eg, severe hypoglycemia, severe allergic reactions, and acute pancreatitis) was between 0.1% and <1% for both lixisenatide and semaglutide, scoring 3 points.

Special Populations

Liraglutide has been approved by the FDA for the treatment of patients with T2DM over the age of 10 years, scoring 0.7. None of the other GLP-1RAs are recommended for use in the pediatric population. None of the 7 GLP-1RAs are recommended in pregnant and breastfeeding populations. In the elderly population, all 7 GLP-1RAs were available, scoring 1 point. In terms of renal dysfunction, exenatide, benaglutide, and PEG loxenatide had no relevant research data, scoring 0 points. Lixisenatide and dulaglutide could be used, scoring 3 points. Liraglutide and semaglutide could be used for mild to moderate renal dysfunction, scoring 2 points. In terms of liver function abnormalities, exenatide, lixisenatide, PEG loxenatide, and semaglutide can be used in mild to moderate, scoring 2 points; liraglutide and dulaglutide can be used in mild, moderate, and severe, scoring 3 points; and benaglutide is not recommended for patients with liver function abnormalities, scoring 0 points.

Drug Interactions

All 7 GLP-1RAs delay gastric emptying, affecting the rate of absorption of drugs absorbed via the gastrointestinal tract, and caution should be exercised in combining with other oral medications to avoid affecting their onset of action, scoring 1 point;

Other

Special dosing warnings were present for all 7 GLP-1RAs, all scoring 0 point. The adverse events that occurred with the 7 GLP-1RAs were largely reversible, scoring 0.5 point. In terms of teratogenicity and carcinogenicity, according to the drug labels, liraglutide, dulaglutide, lixisenatide, and semaglutide are teratogenic and carcinogenic, scoring 0 points;

benaglutide is not teratogenic but lacks data from carcinogenicity studies, scoring 0.5 points; PEG loxenatide is not teratogenic but is carcinogenic, scoring 0.5 points; exenatide is not teratogenic or carcinogenic, scoring 1 point. The safety scores result of the 7 GLP-1RAs are shown in Table 6.

Table 6 Safety Score Results

Safety (25 Points)		Grade	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
Moderate adverse reactions (3 points)	Incidence <1%	3							
	Incidence 1%~<10%	2							
	Incidence≥10%	1	1	1	1	1	1	1	1
	ADR occurrence data not provided	0							
Serious adverse reactions (5 points)	Incidence<0.01%	5							
	Incidence 0.01%~<0.1%	4	4	4		4	4	4	
	Incidence 0.1%~<1%	3			3				3
	Incidence 1%~<10%	2							
	Incidence≥10%	1							
	ADR occurrence data not provided	0							
Special populations (multiple choice, 11 points)	Available for children (2 points for all, 1.9 points for 3 months and older, 1.8 points for 6 months and older, 1.7 points for 9 months and older, 1.6 points for 1 year and older, 1.5 points for 2 years and older, 1.4 points for 3 years and older, 1.3 points for 4 years and older, 1.2 points for 5 years and older, 1.1 points for 6 years and older, 1.0 points for 7 years and older, 0.9 points for 9 years and older, 0.7 points for 10 years and older, 0.6 points for 11 years and older, 0.5 points for 12 years and older). (0.9 points for ages 9+, 0.8 points for ages 9+, 0.7 points for ages 10+, 0.6 points for ages 11+, and 0.5 points for ages 12+).	2	0	0.7	0	0	0	0	0
	Available for the elderly (1 point for available, 0.5 point for caution).		1	1	1	1	1	1	1
	Available for women during pregnancy (1 point for early pregnancy, 0.8 points for mid-pregnancy, 0.5 points for late pregnancy).		0	0	0	0	0	0	0
	Available for lactating women (1 point for availability, 0.5 points for caution).		0	0	0	0	0	0	0
	Abnormal liver function available (3 points for severe available, 2 points for moderate available, 1 point for mild available).		2	3	2	0	3	2	2
	Abnormal kidney function available (3 points for severe, 2 points for moderate, 1 point for mild).		0	2	3	0	3	0	2
Adverse reactions due to drug interactions (3 points)	No dosage adjustment required	3							
	Dose adjustment required	2							
	Prohibition of use during the same period of time	1	1	1	1	1	1	1	1
Other (multiple choice, 3 points)	Adverse effects are reversible	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	No teratogenicity or carcinogenicity	1	1	0	0	0.5	0	0.5	0
	No special medication warnings	1	0	0	0	0	0	0	0
The results of safety		/	10.5	13.2	11.5	8	13.5	10	10.5

Economy

All 7 GLP-1RAs were nationally negotiated drugs, and the prices of the target drugs were finally obtained by referring to the latest negotiated drug prices of the National Health Insurance (2024). The basic economy Information of 7 GLP-1RAs are shown in Table 7. The economy score results are shown in Table 8.

Other Attributes

National Health Insurance and National Essential Drug Characteristics

All 7 GLP-1RAs are in Class B of the National Health Insurance and all have payment restrictions. Liraglutide is included in the National Essential Drug Catalog and has no Δ requirement, and the other 6 GLP-1RAs are not included in the National Essential Drug Catalog.

National Centralized Drug Procurement and Original Research Drugs

All 7 GLP-1RAs are originator drugs, all scored 1 point. In addition, none of the GLP-1RAs are national centralized drug procurement drugs, scoring 0 points.

Market and Business Characteristics

The other 5 GLP-1RAs are available in the United States, Europe, and Japan, except for benaglutide and PEG loxenatide, which are currently available only in China. The manufacturers of exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide are among the top 50 pharmaceutical companies in terms of global sales and are ranked 9th, 15th, 8th, 13th, and 15th, respectively (2022 rankings). PEG loxenatide is ranked 31st in the list of the top 100 pharmaceutical industry of the Ministry of Industry and Information Technology of China. Benaglutide is not in the list of the top 100 pharmaceutical industry in China and World's top 50 pharmaceutical companies. The other attributes score results are shown in Table 9.

Final Scoring Results for the Five Dimensions of the 7 GLP-1RAs

Table 10 displays the final scores for the 7 GLP-1RAs evaluated. The top three GLP-1RAs were obtained by semaglutide, dulaglutide and liraglutide. Meanwhile, they were significantly better than other GLP-1RAs in terms of efficacy.

Discussions

The results of this study showed that the 7 GLP-1RAs were ranked from highest to lowest as semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide, PEG loxenatide, and benalutide. The top 3 rankings of semaglutide (71.5 points), dulaglutide (68.9 points), and liraglutide (68.7 points) were used as preferred drugs.

In addition to being effective and safe, GLP-1RAs provide weight loss and cardiovascular benefits.[25] In terms of weight loss, the FDA has approved the use of semaglutide 2.4 mg and liraglutide 3.0 mg for weight management in patients with overweight or obesity. Studies have shown[26] that weight loss of up to 12.47 kg and 5.24 kg, respectively, can be achieved after more than 20 weeks of treatment with semaglutide 2.4 mg and liraglutide 3.0 mg. In addition, tirzepatide 15 mg showed greater reductions in glycated hemoglobin and body weight compared with semaglutide. All current hypoglycemic agents with cardiovascular benefit are liraglutide, dulaglutide, and semaglutide for GLP-1RAs, and empagliflozin, canagliflozin, and dapagliflozin for SGLT-2i, respectively.[27,28] Meanwhile, adequate vitamin D supplementation may improve insulin resistance in T2DM, as the average age of diabetics is 50–60 years.[29] In clinical practice, it is crucial to select a GLP-1RA with cardiovascular efficacy, good glucose lowering and weight loss according to the patient's condition and needs.

The study conducted by Qiu Bo et al[30] on health technology assessment has been implemented in their region and is now being adopted in other regions of China to provide guidance to healthcare organizations on drug selection based on this guideline. The current evaluation of the 7 GLP-1 RAs was based on the second version of the guideline, which is consistent with the previous evaluation of the first version, which recommended semaglutide (71.00 points), dulaglutide (68.75 points), and liraglutide (67.50 points) as the recommended drugs.[31] With further updates to the guidelines and support from other high-quality evidence-based medicine, the results of the two assessments are consistent, indicating that the results of this health technology assessment are reliable, and representative.

Table 7 The Basic Economy Information of 7 GLP-1RA

Economy	Exenatide	Liraglutide	Lixisenatide	Benaglutide	Dulaglutide	PEG Loxenatide	Semaglutide
Drug specification	1.2mL/piece (0.25mg/mL); 2.4mL/piece (0.25mg/mL);	3mL:18mg	0.05mg/mL, 3mL/piece;0.10mg/mL, 3mL/piece;	2.1mL:4.2mg(42000U)	0.5mL:1.5mg	0.5mL:0.1mg; 0.5mL:0.2mg	1.34mg/mL, 1.5mL/piece;1.34mg/mL, 3mL/piece;
Therapeutic dose	5μg 2 times daily for 1frist month; 10μg 2 times daily for 2nd to 7th month	0.6 mg daily for week 1; 1.2mg daily for week 2; 1.5mg daily for weeks 3–26	10μg daily for 1–2 weeks; 20μg daily for 3–24 weeks	0.1mg (50μL) 3 times/day for 1–2 weeks; 0.2mg (100μL) 3 times/day for weeks 3–12	0.75 mg weekly for 1–2 weeks; 1.5 mg weekly for 3–26 weeks	0.1mg weekly for 1–24 weeks	0.25mg weekly for 1–4weeks; 0.5mg weekly for 5–8weeks; 0.75mg weekly for 9–30weeks
Average daily treatment cost (¥)	12.80	27.38	17.26	25.03	20.47	15.71	16.63

Notes: Therapeutic dose according to the drug instructions, guidelines, expert consensus and consult the relevant literature where the recommended dose of hospital medication (starting dose + maintenance dose calculation). The medication cycle is the main treatment core week of the clinical trial according to the drug instructions. The maintenance dose of liraglutide injection of 1.5 mg / day is based on its clinical use of the average of 1.2 mg / day and 1.8 mg / day; The maintenance dose of semaglutide injection of 0.75 mg / week is based on its clinical use of the average of 0.5 mg / week and 1.0 mg /week.

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Table 8 Economy Score Results

Economy (10 Points)		Grade	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
Economy of the primary indication (10 points)	Evaluation method: 10 points for the drug with the lowest average daily cost of treatment, evaluation drug score = (lowest average daily cost of treatment / average daily cost of treatment of the evaluated drug) × 10	10	10	4.7	7.4	5.1	6.3	8.1	7.7
The results of economy		/	10	4.7	7.4	5.1	6.1	8.1	7.7

Table 9 Other Attributes Score Results

Other Attributes (10 Points)		Grade	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
National Health Insurance (3 points)	NHI Category A, no payment restrictions	3							
	NHI Category A with payment restrictions	2.5							
	NHI Category B, no payment constraints	2							
	NHI Category B with payment constraints	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Not on the NHI list	1							
National essential drugs (3 points)	National essential drugs, no Δ requirement	3		3					
	National essential drugs with Δ requirements	2							
	Not on the National Essential Drug List	1	1		1	1	1	1	1
National centralized procurement of medicines (1 point)	Selected medicines for centralized national procurement	1	0	0	0	0	0	0	0
Original research/ reference/consistency evaluation (1 point)	Drug of origin/reference	1	1	1	1	1	1	1	1
	Passing the consistency evaluation of generic drugs	0.5	0	0	0	0	0	0	0
Status of production enterprises (1 point)	World's top 50 pharmaceutical companies in terms of sales volume / Ministry of Industry and Information Technology's top 100 companies in the pharmaceutical industry (Top 50 pharmaceutical companies in world sales 1–10 1, 11–20 0.8, 21–30 0.6, 31–40 0.4, 41–50 0.2; Ministry of Industry and Information Technology Pharmaceutical Industry Top 100 list) (enterprises 1–20 1, 21–40 0.8, 41–60 0.6, 61–80 0.4, 81–100 0.2)	1	1	0.8	1	0	0.8	0.8	0.8
Global usage (1 point)	Available in China, USA, Europe, Japan	1	1	1	1	0	1	0	1
Other attribute scores		/	5.5	7.3	5.5	3.5	5.3	4.3	5.3

Notes: NHI: National Health Insurance; The "Δ" sign indicates that the drug should be used by a physician with corresponding prescription qualifications or under the guidance of a specialist physician, and use monitoring and evaluation should be strengthened.

The American diabetes association guidelines (2023) and the Chinese guidelines for the prevention and treatment of type 2 diabetes (2020) recommend that among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a SGLT-2i or GLP-1RA with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. Liraglutide, semaglutide and dulaglutide have been shown to be GLP-1RAs with cardiovascular benefit. The results of

Table 10 Final Score Results for the 7 GLP-1RAs

Evaluation Dimension	Exe	Lira	Lixise	Bena	Dula	PEG-loxe	Sema
Pharmacological properties	21.5	21.5	22	20.5	22.5	22.5	23
Efficacy	15	22	13.5	8	21.5	11	25
Safety	10.5	13.2	11.5	8	13.5	10	10.5
Economy	10	4.7	7.4	5.1	6.1	8.1	7.7
Other attributes	5.5	7.3	5.5	3.5	5.3	4.3	5.3
Total (100 points)	62.5	68.7	59.9	45.1	68.9	55.9	71.5

this study show that the results based on the current evaluation are consistent with the recommended results of the guidelines.

The aim of this study was to conduct an objective and rapid evaluation of 7 GLP-1RAs that have been marketed in China to alleviate the selection pressure of medical institutions due to the large number of varieties and to provide an evidence-based basis for selecting drugs. Meanwhile, the study can also provide drug selection recommendations and methodological references for healthcare organizations in other countries, especially in other countries with low and middle incomes or a low level of healthcare. However, there are several limitations to this study: First, this study is a rapid assessment, not a comprehensive. Healthcare organization must take into account its own hospital and local practices when introducing GLP-1RAs. Second, with the updating of evidence-based medicine, the extension of the clinical application period of drugs, the price changes brought about by the tendering and purchasing of drugs, the adjustment of the national essential drug list, the adjustment of the national health insurance list, and the development of drug manufacturers, the changes will further affect our evaluation indexes and results. Therefore, evaluators must update their evaluations in a timely manner to avoid bias in evaluation results.

This study needs more adequate evidence of evidence-based medicine (eg, real-world multicenter clinical data, high-quality meta-analysis, etc.) to make the evaluation results more comprehensive and representative. At the same time, in order to make this guideline more convincing and representative, the weights of each index and evaluation criteria need to be optimized through continuous practice.

Conclusions

7 GLP-1RAs that have been marketed in China were objectively evaluated according to the drug evaluation guidelines, and the evaluation results can provide a reference for medical institutions to select GLP-1RAs drugs. When a healthcare organization introduces a GLP-1RAs, the top three ranked drugs, semaglutide, dulaglutide and liraglutide, can be used as recommended drugs based on the evaluation results.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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