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REVIEW

GLP-1 Receptor Agonists for Type 2 Diabetes and Their Role in Primary Care: An Australian Perspective

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ABSTRACT

The ever-increasing number of drugs available to treat type 2 diabetes and the complexity of patients with this condition present a constant challenge when it comes to identifying the most appropriate treatment approach. The more recent glucagon-like peptide-1 receptor agonists (GLP-1RAs) are non-insulin injectable options for the management of type 2 diabetes. Effective at improving glycaemic control with a low intrinsic risk of hypoglycaemia and the potential for weight reduction, this agent class is an important addition to the prescribing armamentarium. However, understanding their place in therapy may prove confusing for many primary care practitioners, especially given the common belief that 'injectables' are a last-resort treatment option, which puts them at risk of being niched alongside insulin. This review summarises the clinical evidence for GLP-1RAs and how they compare to other glucose-lowering agents in managing type 2 diabetes. It also provides practical and case-driven opinions and recommendations on the optimal use of GLP-1RAs by discussing important patient factors and clinical considerations that will help to identify those who are most likely to benefit from this class of agents.
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INTRODUCTION

Despite the availability of an increasing number of agents for treating type 2 diabetes mellitus (T2DM), as many as half of all T2DM patients are failing to meet their glycaemic goals [1]. This paradox may reflect a treatment landscape that appears complex and confusing, making it difficult for practitioners to identify the right drug for the right patient. Moreover, clinical inertia, including a reluctance to use injectable therapies,

may also be compromising optimal treatment selection and thus clinical outcomes [2, 3].

GLP-1RAs are a relatively new class of injectables that are effective at reducing HbA_{1c}, have a low risk of hypoglycaemia when given as monotherapy or in the absence of sulphonylureas (SU) or insulin, and have the potential for weight loss—key considerations when treating a typical obese patient with T2DM [4]. In addition, individual GLP-1RAs have been developed to overcome common barriers to self-injection by offering a lower injection burden (i.e. weekly vs. daily injections) and devices with a 'hidden' pre-attached needle (e.g. dulaglutide) [5, 6].

Nonetheless, current clinical practice in managing T2DM using GLP-1RAs is likely to vary worldwide due to differences in healthcare systems and their accessibility, in the availability and affordability of medications, as well as in country-specific reimbursement policies. For instance, Australia differs to other regions (such as the USA) where patients are responsible for almost all of their healthcare costs in having a publicly funded healthcare insurance system that provides a rebate for doctor and specialist visits, blood tests and X-rays, although it should be noted that the rebate does not always cover the full cost of medical services, and patients incur 'out-of-pocket' expenses. Also, Australia, the USA and the UK differ in the GLP-1RAs that have received regulatory approval. Among those currently available in Australia, not all are eligible for government reimbursement. Adding to the complexity are the criteria for a subsidised GLP-1RA, which can limit the choice of additional or add-on therapies; e.g. at present, the government will not subsidise a GLP-1RA if given with an insulin. This therefore affects the prescribing patterns of GLP-1RAs in Australia.

In other regions, e.g. Asia or the Middle East, access to and the use of GLP1-RAs are primarily driven by whether the patient can afford it.

Five GLP-1RAs are available in Australia (dulaglutide, exenatide BD, exenatide QW, liraglutide, and lixisenatide), one is undergoing regulatory approval (semaglutide), and three are currently available under the government's reimbursement scheme (dulaglutide, exenatide BD, and exenatide QW). The aim of this article is to explore their clinical rationale, assess where they fit in the current guideline approach and identify which patients may derive benefit from their use. This will allow practitioners to be better informed about why, when and how to treat T2DM with GLP-1RAs appropriately. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CLINICAL RATIONALE FOR GLP-1RAS IN T2DM

It is well recognised that T2DM is a complex and multifactorial disorder attributable to the eight underlying pathophysiological defects labelled the 'ominous octet' [7]. Involving multiple organs, these abnormalities collectively drive the clinical manifestation of the disease (i.e. hyperglycaemia) [7]. The importance of targeting the underlying pathophysiology of T2DM rather than focusing management on reducing plasma glucose levels, as is currently recommended, has recently been debated [8]. It was argued that therapeutic guidelines fail to achieve sustained HbA_{1c} reductions and therefore treatment should be based on addressing pathophysiological defects [8]. In this context, GLP-1RAs are able to target six of these biological abnormalities, whereas other agents such as metformin target mainly one (Fig. 1) [7, 8].

Fundamentally, GLP-1RAs work by stimulating insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner [9], which explains their associated low risk of hypoglycaemia. Importantly, GLP-1RAs are able to improve β-cell sensitivity to glucose and have the ability to improve the glycaemic profile indirectly by delaying gastric emptying, inhibiting hepatic glucose production and suppressing appetite, thereby promoting weight loss [9–11].

GUIDELINE RECOMMENDATIONS ON GLP-1RAS

When and Where Do GLP-1RAs Fit into Current Management?

As different classes of drugs target different aspects of T2DM via distinct mechanisms of

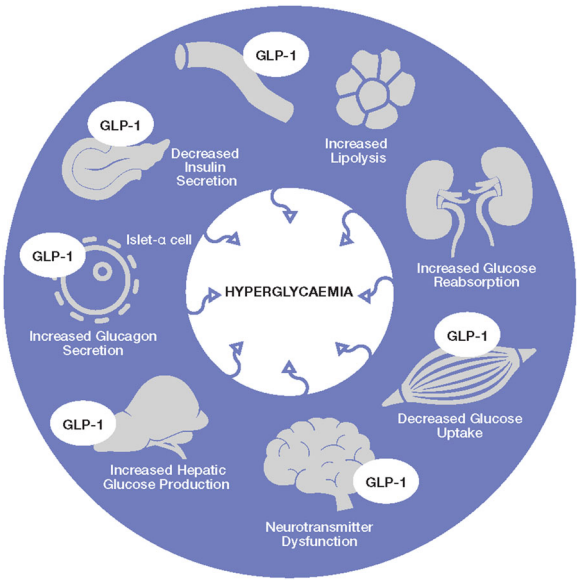

Fig. 1 Pathophysiological targets of GLP-1RAs in T2DM. Adapted from Defronzo [7]

action, a combination of treatments is generally more effective at maintaining glycaemic control than monotherapy over the long term [12]. Indeed, Australian guidelines recommend GLP-1RAs as an add-on option to metformin from the second-line setting (Fig. 2) [13, 14], dispelling the common notion that injectable therapies are a 'last resort' or restricted only to those individuals who fail to respond to maximal doses of oral agents. These guidelines, however, do not give a preference regarding which of the second-line agents—which also include sulfonylureas (SU), dipeptidyl peptidase-4 inhibitors (DPP-IV), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), insulin, thiazolidinediones (TZD) and acarbose—should be added to optimised metformin [13, 14]. In contrast, recommendations for treatment selection in the second-line setting have been outlined in international guidelines, such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines, which inform choice of treatment according to an individual's CV and chronic kidney disease (CKD) risk [15]. Given the increasing availability of CV safety outcomes data for glucose-lowering medications, it has become apparent that certain agents within the GLP-1RA and SGLT-2 inhibitor classes reduce the risk of CV events in those with high-risk CV or CKD [16–21]. With respect to GLP-1RAs, liraglutide and semaglutide have demonstrated a reduction in the risk of major adverse cardiovascular events (MACE) [16, 17], and, while yet not published, early reports for dulaglutide indicate CV benefits in patients with a wide range of CV risk [18]. It is important to note that while GLP-1RAs have demonstrated CV safety, not all result in an actual reduction in CV adverse events, such as exenatide QW and lixisenatide, both of which were reported to be non-inferior to placebo for MACE [22, 23].

Treatment selection should therefore take into consideration efficacy, adverse event profile, hypoglycaemia risk, weight control, presence of comorbidities and CV/CKD risk, as well as cost to patient [13–15, 24].

Case Scenario to Guide Second-Line Treatment Selection

A 52-year-old man with a three-year history of T2DM presents for a review. His current HbA_{1c} is 8.0% (64 mmol/mol) and he weighs 109.7 kg (BMI: 35.1 kg/m^2), which have increased since his last review a year ago. He is receiving a maximal daily dose of metformin extended release (2000 mg; nocte). He also has a history of hypertension and dyslipidaemia that are being successfully managed with amlodipine, low-dose aspirin and atorvastatin. He works in construction in a hot environment.

Suboptimal glycaemic control and increasing weight gain—major risk factors for blood glucose and CV complications—are key concerns for this patient. How would the addition of a GLP-1RA compare to other second-line add-on therapies in improving management of the T2DM?

A review of head-to-head clinical trials comparing key outcomes of using GLP-1RAs (dulaglutide, exenatide BD, exenatide QW, liraglutide or lixisenatide) with those of using DPP-IV (sitagliptin), SU (glimepiride; glibenclamide), TZD (rosiglitazone; pioglitazone) and

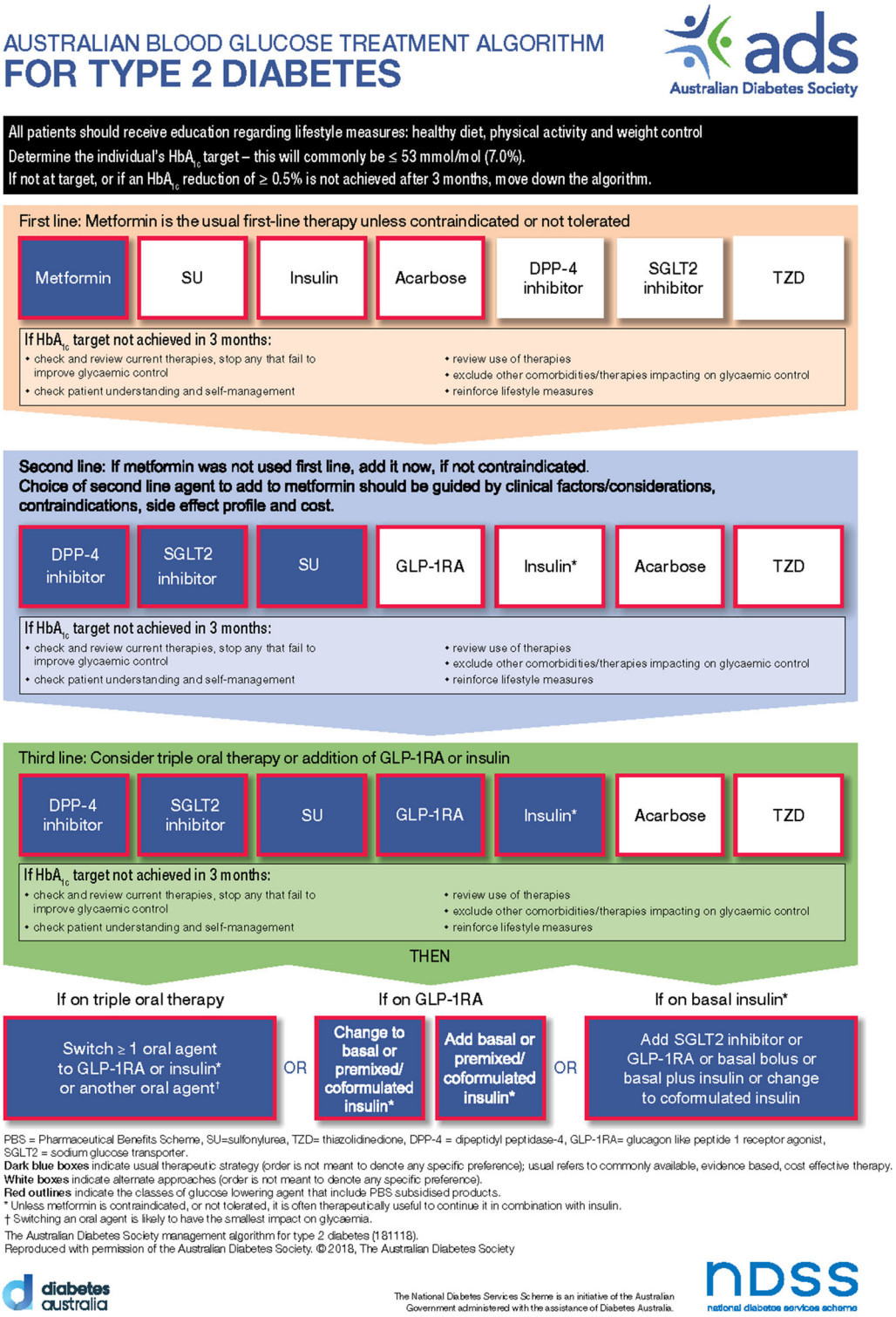

Fig. 2 Where GLP-1RAs fit into current T2DM guidelines. Reproduced with permission from the Australian Diabetes Society

insulin (insulin aspart; insulin glargine) on a background of metformin monotherapy is outlined in Table A below [25]. Note, no head-to-head studies of GLP-1RAs and SGLT-2 inhibitors or acarbose are available.

Given that there are few head-to-head studies comparing glucose-lowering effects between different drug classes, and the difficulty involved in performing cross-study comparisons due to different patient characteristics and

Table A: GLP-1RAs versus other glucose-lowering agents: key specific features that impact treatment choice

	HbA_{1c} reductions (%)	Body weight changes (kg)	GI side effects	Hypoglycaemia[a] rate
GLP-1RA vs. OADs				
DPP-IV [26–30]	0.7 to 1.8 vs. 0.3 to 0.9[b]	− 2.3 to − 3.7 vs. − 0.8 to − 1.8[f]	Greater or similar to DPP-IV	Minor episodes low for both No difference between classes Severe episodes rare*
SU [31–35]	0.4 to 1.5 vs. 0.2 to 1.8[c]	− 2.8 to − 8.0 vs. + 0.7 to + 4.3[f]	Greater than SU	Minor episodes lower than SUs No severe episodes reported**
TZD [26, 36]	− 0.9 to − 1.5 vs. − 1.0 to − 1.2[d]	− 2.3 to − 2.8 vs. + 1.5 to + 2.8[f]	Greater than TZD	Minor episodes slightly greater or similar to TZD Severe episodes rare†
GLP-1RA vs. other injectables				
Insulin [37–40]	− 1.0 to − 1.8 vs. − 0.9 to − 1.9[e]	− 2.5 to − 4.1 vs. + 0.8 to + 2.3[f]	Greater than insulins	Minor episodes generally lower‡ Severe episodes rare§

Data are based on a systematic review (Levin et al. [25]). All drugs were given on a background of metformin only; insulin studies included metformin only or ± SU or ± pioglitazone. Values represent levels of effect across different clinical trials

[a] Definition of minor hypoglycaemia varied between studies from < 3.0 mmol/L (54 mg/dL) to < 4.0 mmol/L (72 mg/dL); severe hypoglycaemia was commonly defined as an episode that required assistance

[b] With the exception of one study (lixisenatide vs. sitagliptin), comparisons indicated significant differences ($p \leq 0.001$)

[c] No significant differences

[d] Comparison indicated a significant difference in one of two studies (exenatide QW vs. pioglitazone) ($p < 0.05$)

[e] Comparisons indicated significant differences in favour of GLP-1RA in two studies ($p < 0.05$ and $p \leq 0.001$) and in favour of insulin in one study ($p < 0.05$)

[f] Comparisons indicated significant differences ($p \leq 0.001$)

* 1 major episode reported for 1.2 mg liraglutide in this selection of studies

** In these selection of studies

† 1 case reported with exenatide plus rosiglitazone in this selection of studies

‡ No difference reported between exenatide vs insulin detemir

§ 2 cases reported for liraglutide in this selection of studies

baseline HbA_{1c} levels, there is widespread consensus that GLP-1RAs are more efficacious at lowering blood glucose than either DPP-IVs or SGLT-2 inhibitors. The expected glucose-lowering efficacy is an important consideration when changing from one glucose-lowering agent to another or when adding a new agent to existing therapy.

So, while DPP-IVs may offer a better gastrointestinal (GI) adverse event profile than GLP-1RAs, they are generally less effective at reducing HbA_{1C} and have a lower potential for weight loss. SUs are as effective as GLP-1RAs in HbA_{1C} reduction and have fewer GI effects, but they can lead to weight gain and also a higher risk of hypoglycaemia, which this patient needs to avoid. Similarly, TZDs are as effective as GLP-1RAs in HbA_{1C} reduction, have fewer GI effects and may have a lower hypoglycaemia risk, but can cause weight gain.

Insulins lead to marked HbA_{1c} reductions and have a lower risk of GI effects but can lead to weight gain and are generally associated with a higher risk of hypoglycaemia than GLP-1RAs, which would present significant occupational implications for this patient. While insulins and GLP-1RAs have been considered equally effective at reducing HbA_{1c} [41, 42], a more recent meta-analysis reported that long-acting, once-weekly GLP-1RAs (exenatide and dulaglutide) achieve significantly greater reductions in HbA_{1c} than basal insulins such as insulin detemir, insulin glargine and insulin degludec [43]. However, insulin was found to be more effective at reducing fasting plasma glucose but less effective at reducing postprandial glucose levels than GLP-1RAs [42, 44]. Several systematic reviews also indicated that GLP-1RAs are consistently effective at reducing body weight [25, 41, 42, 44], supporting the nonglycaemic role of this agent class [44], as opposed to the weight gain that commonly accompanies insulin treatment [44]. Furthermore, the risk of hypoglycaemia—a major challenge when using insulin—is reportedly lower with GLP-1RAs, given their glucose-dependent mechanism of modulating insulin release and glucagon suppression [25]. Alongside these benefits of GLP-1RAs, however, is an increased propensity for GI adverse events, notably nausea, when compared with insulin. Table 1 outlines these comparisons further.

Table 1 GLP-1RAs versus insulin

Features/effects	GLP-1RA vs insulin	
HbA_{1c} reduction (%)	Similar (0.6–1.6%)[‡]	Similar (0.6–1.3%)
Weight change (kg)	Weight reduction (up to − 2.6 kg)	Weight gain (up to + 3.7 kg)
Hypoglycaemic risk*	Lower risk[†]	Higher risk
Fasting plasma glucose reduction	Less effective	More effective
Frequency of injections	Twice-daily; once-daily or once-weekly	Multiple daily injections

* Based on Australian product labels for dulaglutide, exenatide BD and exenatide QW

† Concomitant use of SU or insulin can increase risk of hypoglycaemia

‡ vs. basal insulin and when used in patients with a baseline HbA1c of ~ 8% (~ 64 mol/mol) [46]

Given that weight control and a low risk of hypoglycaemia are key considerations for this patient, the addition of a GLP-1RA may be the most appropriate choice. This selection is further supported by the CV outcomes data for specific GLP-1RAs, which point to benefits in reducing the risk of MACE in at-risk individuals [16–18]. The most appropriate GLP-1RA to use will ultimately be dictated by the device and how it aligns with the patient's needs, as well as associated costs and the reimbursement status of the drug options.

INDIVIDUALISING CARE: CHOOSING THE RIGHT GLP-1RA FOR THE RIGHT PATIENT

Not All GLP-1RAs are Made Equal

GLP-1RAs are often differentiated according to structure and duration of action (Table 2)

Table 2 Short versus long-acting GLP-1RAs

Features/effects	Short-acting (exenatide BD, liraglutide QD, lixisenatide QD)	Long-acting (dulaglutide QW, exenatide QW, semaglutide QW*)
Peptide backbone	Exendin-4	Human GLP-1 (dulaglutide, semaglutide) Exendin-4 (exenatide QW)
Fasting plasma glucose	++	+++
Postprandial plasma glucose	+++	++
Gastrointestinal effects	+++	++
Adherence potential	+	++/+++
Injection burden	+++	+

+ = low, ++ = medium/moderate, +++ = high/strong
* Semaglutide has not yet received regulatory approval in Australia

[9, 24, 45–48]. In terms of structure, several GLP-1RAs have been developed based on the naturally occurring protein exendin-4 (from the Gila monster, a lizard found in New Mexico and Arizona), which shares 53% homology with native (human) GLP-1 [49–51]. Other GLP-1RAs have exploited the native GLP-1 molecule with 90–97% homology and modifications to resist degradation by the enzyme DPP-IV [35, 48].

GLP-1RAs can also be differentiated according to their duration of receptor activation. Short-acting agents undergo renal clearance, so they require once-daily (lixisenatide) or twice-daily (exenatide BD) dosing. Long-acting agents, on the other hand, provide continuous receptor activation due to structural modifications that slow their absorption, reduce the rate of renal clearance or extend their half-lives [52, 53]. These GLP-1RAs include once-weekly dulaglutide, exenatide and semaglutide (yet to be approved in Australia) and once-daily liraglutide (Table 2). Differences in the duration of action may also account for their differential effects on fasting and postprandial glucose [54]. For instance, short-acting GLP-1RAs are more strongly associated with delayed gastric emptying than long-acting agents, leading to a greater impact on postprandial glucose. In contrast, the persistent effects of longer-acting GLP-1RAs offer 24-h glucose control, including fasting glucose [53]. As a result, patients with largely postprandial hyperglycaemia are more likely to benefit from treatment with short-acting GLP1-RAs as opposed to individuals with predominantly fasting hyperglycaemia, who would derive greater benefit from long-acting agents [52].

In terms of tolerability, GLP-1RAs are commonly associated with GI side effects, which are often dose-dependent and time-limiting [55]. However, long-acting GLP-1 RAs appear to cause less nausea and vomiting but more diarrhoea than short-acting agents [56]. The frequency of these events is lower with once-weekly GLP-1RAs compared to once-daily or twice-daily GLP-1RAs (Table 2) [57]. Of note, a small number of cases of acute pancreatitis associated with GLP-1RA use have been reported in clinical trials: 38 cases in 17,775 patient-years of exposure compared with 9 events in 5863 patient-years of exposure with the comparator treatment. Resulting pooled event rates were 2.1 and 1.5 per 1000 patient-years of exposure, respectively, and the OR was 1.39 (95% CI 0.67, 2.88), suggesting a slightly elevated risk [58]. In a separate meta-analysis, a significantly increased risk of cholelithiasis (OR 1.30; 95% CI 1.01–1.68; $p = 0.041$) but not pancreatitis or pancreatic cancer was reported for GLP-1RAs compared with comparator treatments [59]. A more recent analysis using cardiovascular outcome trials further indicated no excess risk of either acute pancreatitis [Peto OR 0.89 (95% CI 0.63, 1.27)] or pancreatic cancer [Peto OR 0.84 (95% CI 0.53, 1.35)] with GLP-1RAs vs. placebo when added to the standard of care [60]. An increased risk of diabetic retinopathy has been reported in a clinical trial of semaglutide, which has been hypothesised to be related to the magnitude and rapidity of

glucose lowering [61]; this complication does not appear to be a class-driven effect.

Tackling Adherence Challenges One GLP-1RA at a Time

T2DM management has shifted from a 'one size fits all' approach to a more holistic, patient-centred approach that aligns goals of management, such as glycaemic targets and risk factor control (e.g. weight or CV risk), with patient preferences and characteristics [62]. Involving the patient in treatment decisions also helps with adherence to therapy, which is a major challenge in T2DM. For instance, in an Australian study, approximately a third of patients with T2DM were found to have suboptimal adherence to their diabetes medication [63].

Strategies that address convenience in terms of simplicity of drug regimens, formulations and delivery devices have been shown to improve adherence [64]. Indeed, GLP-1RAs have evolved over time such that the frequency of dosing has decreased from twice-daily (exenatide, BD) [65], to once-daily (liraglutide, lixisenatide) [66, 67] to once-weekly (dulaglutide, exenatide QW, semaglutide) [5, 6], suggesting a higher adherence potential for the longer-acting agents (Table 2). Moreover, improvements in drug formulations (such as those which do not require reconstitution or dose titration) and injection devices with hidden and pre-attached needles, which together serve to reduce treatment complexity, may lead to a more positive injection experience for patients (Table 3) [68].

Indeed, lowering the regimen complexity and treatment burden has been shown to improve treatment satisfaction, which in turn plays an important role in supporting adherence to medication [69]. Data on patient-reported outcomes for individual GLP-1RAs indicate high treatment satisfaction rates with the long-acting agents (Table 3) [69–74], while dulaglutide was associated with higher adherence and persistence rates than exenatide QW and liraglutide [75].

Table 3 Subsidised GLP-1RAs in Australia

GLP-1RA	Pen characteristics					Injection site reactions† (%)	Patient satisfaction with device
	Dosing	Device	Reconstitution	Needle included	Titration		
Dulaglutide [5]	Weekly	Single-dose prefilled pen	No	Yes (hidden)	No	0.7	> 96% reported satisfaction with device
Exenatide BD [65]	Twice-daily	Multidose prefilled pens	No	No	Yes	5.7	Data not available
Exenatide QW [6]	Weekly	Vial with diluent syringe single-dose prefilled pen	Yes	Yes (visible)	No	22	Patients switching from exenatide BD to QW reported significant improvements in total DTSQ-s scores (p = 0.037)

Note: liraglutide and lixisenatide are not government reimbursed
DTSQ-s Diabetes Treatment Satisfaction Questionnaire-status
† Includes pruritis, erythema, haematoma, nodule, induration, pain

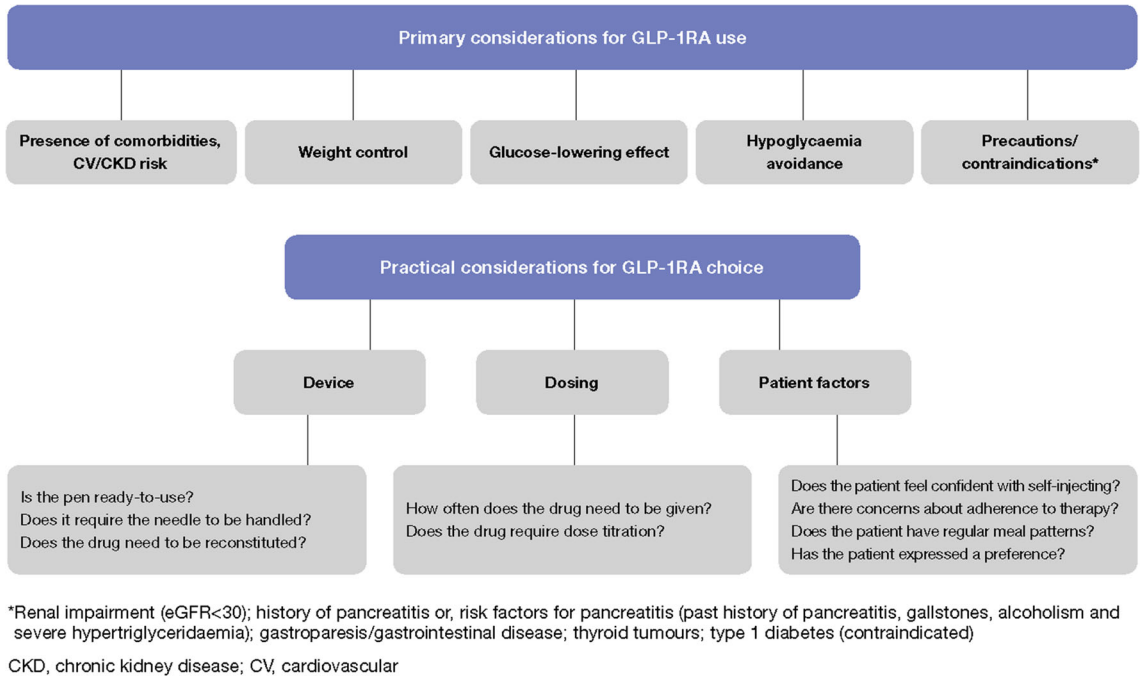

Fig. 3 Clinical decision algorithm

Given the many factors that come into play when deciding on the most appropriate choice of treatment for T2DM in an individual patient, in the context of GLP-1RAs, a clinical decision algorithm that incorporates author opinion is proposed; see Fig. 3 [5, 6, 24, 50].

Practical Considerations for GLP-1RA Use

As GLP-1RAs are injectables, comparisons of GLP-1RAs with insulins are inevitable. However, the practicalities of initiating GLP-1RAs are far less complicated, largely due to the simpler injection devices involved. For those patients who express concerns about injections or lack confidence with self-injections, it would be appropriate for the primary practitioner to demonstrate the ease with which these devices can be used. If needle phobia is a particular issue, discussion of options that have the needle hidden and/or have a pre-attached needle, which require minimal handling by the patient, could be considered.

While most GI side effects (nausea, vomiting and diarrhoea) caused by GLP-1RAs are mild to moderate and short-lived [5, 6, 50], they can be minimised by recommending simple measures such as eating smaller meals, stopping eating as soon as the patient feels full, and injecting at mealtimes. Some GLP-1RAs devices have the ability to easily adjust the dose in response to intolerance (e.g. the liraglutide pen allows for a 0.6-mg dose adjustment) [66, 76].

Diabetes educators and/or practice nurses with a specialty in diabetes are an important point of contact for patient education; such services are particularly valuable to primary practitioners who are time-constrained.

CONCLUSIONS

GLP-1RAs are effective at improving glycaemic control and, by virtue of their mechanism of action, have a low risk of hypoglycaemia combined with the potential for weight loss. Considering that many patients with T2DM are obese, these agents represent important options among the current therapeutic arsenal. From a practical point of view, different GLP-1RAs offer different dosing and device experiences, allowing practitioners to tailor treatment according to the needs of the individual patient.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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