UNIT NO. 1

ORAL GLUCOSE-LOWERING AGENTS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Family physicians manage the majority of patients with type 2 diabetes mellitus (T2DM) in Singapore. Hence, they should be familiar with the profile of the many available oral glucose-lowering agents. These drugs vary in their mechanisms of action, glucose-lowering efficacy, safety profiles and treatment costs between classes – even within classes in some cases. These factors should be carefully considered for a patient-centred approach to selecting oral glucose-lowering therapy. This review aims to describe the characteristics of various oral glucose-lowering agents available to family physicians in the management of T2DM and the impact of these characteristics on the patient-centric approach to treatment decision-making.

Keywords: Type 2 Diabetes Mellitus; Hypoglycemic Agents; Patient-centred Care; Cardiovascular Disease; Sodium-Glucose Transporter 2.

SFP2019; 45(1) : 6-11

INTRODUCTION

The majority of newly diagnosed type 2 diabetes mellitus (T2DM) patients, as well as those with long-standing but well-controlled disease, can be treated in the primary care setting. At present, family physicians have at their disposal an increasing number of therapeutic options for the management of hyperglycaemia in T2DM, including several oral glucose-lowering agents that can be used in an outpatient setting. A growing number of the newer agents have a robust evidence base for their glucose-lowering efficacy, side-effect profile, and, more recently, cardiovascular safety due to the U.S. Food and Drug Administration (FDA) guidance issued in 2008 requiring long-term safety trials for new anti-diabetic drugs. These studies have contributed to a deeper understanding of the real cost-benefit ratios of oral glucose-lowering agents.[1]

The mechanisms of action, glucose-lowering efficacy, safety profiles and treatment costs of the various classes of oral glucose-lowering agents differ between classes, and even within classes for some adverse effects. Several guidelines have since then advocated for a rational and patient-centric approach to the choice of oral glucose-lowering agents in the management of diabetes. Considerations include efficacy and durability of effect, safety and side effects, cost and cost-effectiveness of the various agents, as well as the patient's preferences for therapy and tolerability (Table 1).[2–4]

This review aims to describe the characteristics of various oral glucose-lowering agents available to family physicians in the management of T2DM and the impact of these characteristics on the patient-centric approach to treatment decision-making.

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ORAL GLUCOSE-LOWERING DRUGS FOR FAMILY PRACTICE

Biguanide (Metformin)

Metformin has been used in the treatment of T2DM for over 60 years and is now considered the preferred first-line oral glucose-lowering agent for most patients with T2DM due to its established long-term efficacy and safety.[2,4,5] This time-tested medication exerts its hypoglycaemic effects through multiple mechanisms, namely: (1) direct suppression of hepatic glucose production; (2) suppression of gluconeogenesis through AMP-activated protein kinase activation; (3) inhibition of various gluconeogenic pathways of lactate; and (4) improvement in insulin sensitivity.[5] These effects lead to reductions in glycated haemoglobin (HbA1c) ranging from 1.0 percent to 1.5 percent.[4]

Metformin has an acceptable CV safety profile, as shown in a 2017 meta-analysis involving 2,079 individuals with T2DM treated with either metformin or a comparator (either placebo, diet, sulfonylureas or insulin, depending on the study).[6] This analysis found that metformin did not significantly increase the risk (Mantel–Haenszel relative risk) of all-cause mortality (relative risk [RR] 0.96; 95% confidence interval [CI] 0.84, 1.09); cardiovascular (CV) death (RR 0.97; 95% CI 0.80, 1.16); myocardial infarction (RR 0.89; 95% CI 0.75, 1.06); stroke (RR 1.04; 95% CI 0.73, 1.48); and peripheral vascular disease (RR 0.81; 95% CI 0.50, 1.31).

The recommended dose of metformin is 2,000 to 2,500 mg/day, which should be achieved through slow titration.[2,4] Furthermore, it may promote some weight loss and has a low risk of hypoglycaemia. Its most common adverse effects are nausea, vomiting and diarrhoea, which may be minimised by taking the drug together with meals.

Metformin should be used with caution in patients with renal impairment and those at risk of lactic acidosis, such as those with hepatic impairment or heart failure.

Before starting metformin, obtain the patient's eGFR.

- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2 .

- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m^2 , assess the benefits and risks of continuing treatment.
- Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2 .

Long-term metformin treatment may also cause vitamin B12 malabsorption and/or deficiency in a few patients, which could lead to anaemia or peripheral neuropathy. In these patients, vitamin B12 supplements should be given.[2,4]

Sulfonylureas

This broad group of oral glucose-lowering agents lowers blood glucose by stimulating the secretion of insulin by pancreatic beta-cells.[3] These drugs have good glucose-lowering efficacy (HbA1c reduction of 1.0% to 1.5%), are inexpensive, and are widely available. However, their efficacy is generally not durable and their use is also associated with weight gain. Furthermore, they carry non-negligible hypoglycaemia risks, especially among the elderly and those with renal or hepatic impairment.[4] In Singapore, majority of those who experience severe hypoglycaemia are on sulfonylurea therapy, and 1-year mortality among these patients was 20.7 percent.[8] First-generation sulfonylureas such as chlorpropamide and glibenclamide should be avoided due to their increased hypoglycaemia risk. Second-generation sulfonylureas, such as glipizide and gliclazide, are instead preferred.

The CV safety profile of sulfonylureas remains unclear and is neutral at best.[3,9] Furthermore, a meta-analysis that compared sulfonylurea-based therapy with metformin-based therapy found that the former was associated with inferior CV outcomes compared to metformin.[10] Despite these limitations, sulfonylureas may still be considered a reasonable choice, especially when treatment cost is an important consideration for the patient.

DPP-4 Inhibitors or Gliptins

The dipeptidyl peptidase 4 (DPP-4) inhibitors, also known as gliptins, are incretin-based treatments that have become increasingly popular due to their favourable efficacy and safety profile. These drugs inhibit the enzyme DPP-4, which rapidly degrades glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.[11] This inhibition increases the concentration of the two hormones, which exert a glucose-lowering effect in a glucose-dependent manner.

DPP-4 inhibitors generally reduce HbA1c by around 0.5 percent to 0.8 percent.[4] However, compared to sulfonylureas, these drugs are not associated with hypoglycaemia when used as monotherapy because of their dependence on glucose.[3,11] Furthermore, they do not contribute to weight gain, unlike sulfonylureas and thiazolidinediones.

CV safety trials on DPP4 inhibitors showed that these drugs do not increase the risk of composite adverse cardiovascular outcomes.[12-14] However, the SAVOR-TIMI-53 study showed that saxagliptin was associated with a 27-percent increase in the risk of hospitalisation due to heart failure (hazard ratio [HR] 1.27; 95% CI 1.07–1.51; p=0.007).[11] On the other hand, the EXAMINE trial found that alogliptin was associated with an increased risk of developing heart failure among those without such a background history (HR 1.76; 95% CI: 1.07–2.90).[15] In contrast, the TECOS study found that sitagliptin did not significantly increase the risk of CV events (HR 0.98; 95% CI 0.88–1.09) or hospitalisation due to heart failure (HR 1.00; 95% CI 0.83–1.20; p=0.98).[13] Furthermore, the CARMELINA study provided additional reassuring findings indicating that linagliptin does not significantly increase the risk of CV events or hospitalisation for heart failure.[16]

Rare but distressing safety signals have started to emerge with the increased use of gliptins. There have been reports of patients developing bilateral seronegative polyarthritis after the introduction of DPP-4 inhibitors.[17] However, a 5-year population-based cohort study found no association between DPP-4 inhibitors and severe joint pain (adjusted HR 0.92; 95% CI 0.83-1.02).[18] More recently, there have also been an increasing number of reports implicating DPP-4 inhibitors in the development of bullous pemphigoid.[19] Acute pancreatitis is also a rare but severe adverse effect of DPP-4 inhibitors.[20]

Given these characteristics, local cost-effectiveness analyses have shown that the use of DPP-4 inhibitors, as a component of metformin-based combination therapy, is less cost effective compared to sulfonylureas or sodium-glucose cotransporter 2 (SGLT2) inhibitors.[4] Hence, while DPP-4 inhibitors can be used across a wide range of patients, they are perhaps best reserved for those who cannot receive sulfonylureas (e.g., those with renal impairment) or SGLT2 inhibitors (e.g., those at risk of diabetic ketoacidosis [DKA]).

SGLT2 Inhibitors

This class of oral glucose-lowering agents has significantly changed diabetes management through an insulin-independent mechanism of action: inhibition of glucose reabsorption by renal SGLT2 receptors, hence promoting urinary glucose excretion. This results in HbA1c reductions ranging from 0.6 percent to 0.9 percent, as well as a reduction in body weight through caloric loss via urine and a slight reduction in blood pressure.[4]

Importantly, SGLT2 inhibitors are the first oral glucose-lowering agents to provide CV benefits (lower ischaemic events and hospitalisation for heart failure) and renal protection.[21] In 2015, the EMPA-REG OUTCOME trial found that empagliflozin was associated with a significant reduction in the risk of major adverse cardiovascular events (MACE — comprising CV death, nonfatal myocardial

infarction and nonfatal stroke) compared to placebo in T2DM patients.[22] Three large-scale multinational real-world studies also found that the use of SGLT2 inhibitors was associated with a significant reduction in the risk of CV events.[23-25] The CANVAS/CANVAS-R study also reported similarly favourable CV outcomes associated with the use of canagliflozin.[26]
Of note, the DECLARE-TIMI 58 study demonstrated a reduction in the rate of hospitalisation for heart failure across a wide spectrum of patients with T2DM, regardless of history of established CV disease or prior heart failure.[27] Dapagliflozin also had reassuring safety data with no increased risk of amputations, fractures or Fournier's gangrene.

Overall, SGLT2 inhibitors are appropriate for patients at risk of hypoglycaemia, overweight or obese patients, or those with CV disease. They can also be combined with other oral glucose-lowering drugs and insulin therapy, due to their insulin-independent action. However, SGLT2 inhibitors depend on adequate urinary glucose excretion; hence, these are not appropriate for those with severe renal impairment.[3,4] The dosing recommendations for SGLT2 inhibitors according to eGFR are shown in Table 2.[28-30]

The risks associated with SGLT2 inhibitors include an increased risk of dehydration, postural hypotension, urinary and genital tract infections (Table 3) and DKA.[3,4,31] Furthermore, the CANVAS studies reported an increased risk of bone fractures and lower limb amputations with canagliflozin treatment.[26] Therefore, SGLT2 inhibitors should be used with caution in patients on diuretics and/or renin-angiotensin blockers.[3] SGLT2 inhibitors should be avoided in patients at risk of DKA, such as those with type 1 diabetes mellitus or those with a history of severe hyperglycaemia, recent surgery, infection, low caloric or carbohydrate intake, long-standing T2DM or pancreatic insufficiency.[4] While there are trials on the use of empagliflozin and dapagliflozin in patients with type 1 diabetes mellitus, use on these patients are currently off-label. Patient advice should include good urogenital hygiene and the need for emergency care for those with lower limb pain or symptoms of DKA.

Others

Acarbose is an oral alpha-glucosidase inhibitor that slows down the digestion and absorption of carbohydrates.[3] Hence, it also reduces postprandial glucose excursions and has a low risk for hypoglycaemia. However, its overall glucose-lowering efficacy is modest. Furthermore, it frequently causes adverse gastrointestinal effects, which, together with the need for frequent dosing, has limited its widespread use.

Meglitinides such as repaglinide and nateglinide stimulate insulin secretion and reduce postprandial glucose excursions.[3] With cautious dosing, these drugs are generally safe to use in patients with advanced kidney disease. However, they are seldom used due to frequent dosing and associations with weight gain and hypoglycaemic risk. The cardiovascular safety profile of meglitinides is uncertain.

Thiazolidinediones such as pioglitazone and rosiglitazone improve insulin sensitivity and are associated with good glucose-lowering efficacy.[3] Pioglitazone has also been shown to reduce CV events.[32] However, these agents are associated with fluid retention, congestive heart failure, weight gain and bone fractures, which, together with drug costs, have all limited their use in clinical practice.[3]

Table 1 summarises the characteristics associated with each class of oral glucose-lowering agents.

PATIENT PREFERENCE

Seeking and understanding the different patient preferences for attributes in oral glucose-lowering agents should help to guide conversations between healthcare professions and patients. With a wide variety of treatment options available in Singapore, it is important for us to determine how patient perceptions of specific treatment attributes vary in order to understand how such attributes might affect choices. These conversations will facilitate patient-centred treatment, and hopefully lead to improved patient outcomes, satisfaction and adherence.

CONCLUSION

Most patients with diabetes can be managed effectively and safely in family practice and chronic care. This should be done through holistic care that considers not just glucose-lowering efficacy but also other considerations such as the need for CV and renal protection, patient risk profiles, potential adverse effects and patient preferences. For now, metformin remains the preferred first-line oral therapy for T2DM but SGLT2 inhibitors show much promise in providing clinical benefits beyond glycaemic control.

Declaration of Conflicts of Interest

The author declares no conflict of interest in relation to this article and thanks MIMS for editorial assistance.

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Table 1: Available oral glucose-lowering agents in Singapore[2-4]

Drug class	Patient profile	Efficacy and other salubrious effects	Cost	Safety and side effects
Biguanides (metformin)	Most patients as first-line therapy	High efficacy Weight loss	$–$$	• Neutral CV safety • Low risk of hypoglycaemia • Most common adverse effects are nausea, vomiting and diarrhoea (take with meals) • Vitamin B12 deficiency (supplement) • Use with caution: (1) renal impairment; (2) at risk of lactic acidosis (e.g., hepatic impairment, heart failure • Avoid: eGFR <30 mL/min/1.73 m^2
Sulfonylureas	When cost is a major consideration	High efficacy	$	• Weight gain • Hypoglycaemia • Uncertain CV risk
DPP-4 inhibitors	• Cannot receive sulfonylureas (e.g., renal impairment) • Cannot receive SGLT2 inhibitors (e.g., at risk of DKA)	Intermediate efficacy	$$$	• Weight neutral • Low hypoglycaemia risk • Saxagliptin and alogliptin show signals for increased risk of hospitalisation for heart failure • Rarely, arthritis, bullous pemphigoid, acute pancreatitis • Reduce dose for renal impairment (except linagliptin)
SGLT2 inhibitors	• At risk of hypoglycaemia • Obese or overweight • Cardiovascular disease	Intermediate efficacy Weight loss Slight blood pressure reduction CV protection	$$	• Postural hypotension or dehydration • Urinary or genital infections • DKA • Rare: risk of lower limb amputation or bone fractures (canagliglozin) • Avoid: severe renal impairment and those at risk of DKA
Alpha glucosidase inhibitors	Seldom recommended	Low-intermediate efficacy Reduces postprandial glucose excursion	$$	Frequently causes gastrointestinal adverse effects
Meglitinides	Use with caution in advanced kidney disease	Intermediate efficacy Reduces postprandial glucose excursion	$$	Meglitinides such as repaglinide and nateglinide stimulate insulin secretion and reduces postprandial glucose excursions.[3] With cautious dosing, these drugs are generally safe to use in patients with advanced kidney disease. However, they are seldom used due to frequent dosing and associations with weight gain and hypoglycaemic risk. The cardiovascular safety profile of meglitinides is uncertain.
Thiazolidinediones	Seldom recommended	Intermediate - high efficacy Pioglitazone may reduce CV events	$$	• Fluid retention, congestive heart failure, weight gain and bone fractures • Rosiglitazone may increase the risk of CV events

CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; HbA1c, eGFR, estimated glomerular filtration rate; haemoglobin A1c; PECS, patient, efficacy, cost/cost effectiveness, safety and side effects; SGLT2, sodium-glucose cotransporter 2.

Table 2: Recommended dosing of SGLT2 inhibitors by renal function[28-30]

Estimated glomerular filtration rate	Dapagliflozin	Empagliflozin	Canagliflozin
>60	10mg	10mg or 25mg	100 mg or 300 mg
45 to 59	10mg	10mg dose only	100 mg
<45	Not recommended	Not recommended	Not recommended

Table 3: Number of adverse event reports of genitourinary infections submitted to the Health Sciences Authority by public healthcare institutions and the drug utilisation rates of the different SGLT2 inhibitors

SGLT2 inhibitor agent	Number of reports	DDD*	Reports/million DDD
Canagliflozin	1	419,370	2.38
Dapagliflozin	3	1,084,636	2.76
Empagliflozin	5	764,430	6.54

**DDD: Defined daily dose for public healthcare institutions & Raffles Hospital; 2014–Sept 2017*
The information above is to provide a crude baseline comparison between the number of reports received with the utilisation of SGLT2 inhibitors. The data provided should not be used to draw comparisons on the safety of different brands of SGLT2 inhibitors as this is confounded by factors such as extent of use, the patient populations exposed and under-reporting. It does not include private hospital reports. It does not represent a risk assessment of this class of drugs.

LEARNING POINTS

- **A patient-centred approach should guide the choice of pharmacotherapy. Considerations include patient preferences and characteristics, comorbidities, hypoglycaemia risk, impact on weight / cardiovascular and renal outcomes, cost and side effect profile.**
- **Metformin is the preferred initial agent. Newer classes like SGLT2 inhibitors are reasonable alternatives / add-ons in view of the potential for cardiovascular and renal benefits. Sulphonylureas are also considered in view of availability and low costs.**
- **Timely re-evaluation of pharmacotherapy regimen, patient factors and treatment goals is key.**