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Choosing the Best Oral Diabetic Agents in T2 Diabetes Mellitus-Physicians Challenge

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Abstract

The therapeutic armamentarium of oral diabetic agents has expanded its horizon from sulfonylureas in 1995 the only drug available for treating type 2 diabetes mellitus at that time to eleven classes of oral diabetes agents at present ranging from biguanides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha glucosidase inhibitors and sodium-glucose cotransporter (SGLT2) inhibitors. Despite the availability of so many options glycemic control remains suboptimal posing a real challenge for the clinicians to choose the best amongst them in treating type 2 diabetes mellitus.

Before choosing the drugs it is important to know the recommendations of glycemic goals in adults. A reasonable glycosylated hemoglobin (A1C) goal in adult is <7%. However all glycemic goals should be individualized and customized. Setting individual glycemic goals needs consideration of several factors like risk of hypoglycemia and other adverse effects of drugs, disease duration, age and life expectancy of patients and other individual patient considerations like patients attitude resources and support system. Till today our approach towards diabetes management is GLUCOCENTRIC. The key component being how to achieve glycemic control with minimal side effects. While choosing drugs the factors considered are its efficacy (A1c reduction), risk of hypoglycaemia, effect on weight and other adverse effects, cost, ease of administration and patient's preference. A patient-centered approach is of paramount importance while choosing the pharmacological agents rather that establishing a universally accepted algorithm as this will definitely improve the compliance. The advantages and disadvantages of each class of agents help the practitioners to choose the best options.

Keywords: Diabetes mellitus; A1C; Oral diabetic drugs; Hypoglycemia

Introduction

Good glycemic control remains the cornerstone of managing T2 diabetes mellitus. Such approaches play a vital role in preventing or delaying the onset and progression of diabetic complications. The therapeutic armamentarium of oral diabetic agents has expanded its horizon from sulfonylureas in 1995 the only drug available for treating type 2 diabetes mellitus at that time to eleven classes of oral diabetes agents at present ranging from biguanides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like receptor agonists, an amylin analogue, bromocriptine, bile-acid sequestrant, alpha glucosidase inhibitors and sodium-glucose cotransporter (SGLT2) inhibitors. Despite the availability of so many options it's a real challenge for the clinicians to choose the best amongst them in treating type 2 diabetes mellitus.

The pathophysiological mechanisms underlying T2 diabetes mellitus are reduced insulin secretion from pancreatic β-cells, elevated glucagon secretion from pancreatic α cells, increased hepatic glucose production, neurotransmitter dysfunction and insulin resistance, enhanced lipolysis, increased renal glucose reabsorption, reduced incretin effect in the small intestine, and impaired or diminished glucose uptake in peripheral tissues such as skeletal muscle, liver, and adipose tissue which occurs in isolation or in combination. Currently available glucose-lowering therapies target one or more of these key pathways.

Setting a Target

Good glycemic control is reflected by HBA1C which remains the foundation of managing T2 Diabetes Mellitus. Before choosing the drugs it is important to know the recommendations of glycemic goals in adults. A reasonable A1C goal in adult is <7%. However all glycemic goals should be individualized and customized. Setting individual glycemic goals needs consideration of several factors. The disease related factors are duration of diabetes, age and life expectancy of patients and associated comorbid conditions. The most important drug related factors are adverse effects of drugs specially risk of hypoglycemia. Patient's attitude, resources and support system also helps in deciding individual glycemic targets. More stringent goals (<6.5%) are recommended in people with low risk of hypoglycemia, newly diagnosed cases, long life expectancy, absent co morbidities and vascular complications, patients who are highly motivated, adherent to therapy and with readily available resources and support system. On the other hand less stringent goals (<8%) are targeted for patients with high risk of hypoglycemia, long standing disease, short life expectancy, associated co morbidities, vascular complications and those who are non-compliant or poor self-care capacity and limited resources.

Choice of Drugs

While choosing oral diabetic drugs one must consider its efficacy, potential adverse effects, and effects on weight gain, risk of hypoglycemia, cardio protectiveness and cost of therapy. It is also important to have a patient centered approach to guide the choice of pharmacological agents. The major classes of oral antidiabetic medications include biguanides, sulfonylureas, meglitinides, thiazolidinediones (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and α-glucosidase inhibitors.

If HBA1C is more than or equal to 9% at diagnosis initiation of combination therapy or insulin in parallel with diet and exercise is recommended. The goal is to achieve HBA1C to <6.5% by 6 months. If HBA1C is less than 9% at diagnosis monotherapy is initiated in parallel with diet and exercise. If the A1C is more than 6.5% at 3 months combination therapy is recommended with a goal to achieve A1C to less than 6.5 in 6 months [1,2].

Monotherapy

AS per ADA (American diabetes association) and EASD (European Association for the Study of Diabetes) guidelines metformin is the primary agent of choice. For monotherapy metformin is still the preferred initial pharmacological agent for type 2 diabetes unless contraindicated or not tolerated. This drug has a long-standing evidence base for efficacy and safety, is inexpensive, and has cardio protective effects. The risk for hypoglycemia is low and it causes weight loss too.

Combination Therapy

If A1C target is not achieved after 3 months of monotherapy two drug combination is advocated. Choice depends on patient and disease related factors. The factors being immediate outcome like glycemic control (HBA1C %), effects on body weight, LDL cholesterol, HDL cholesterol and triglycerides levels. Consideration of long term clinical outcomes like all-cause mortality, cardiovascular mortality and microvascular outcomes are equally important before choosing the drugs. The most important factor in choosing the drug is their adverse effects like mild to moderate hypoglycemia, gastro intestinal intolerance, congestive heart failure, liver injury etc. Metformin can be added with other drugs. Choosing the agents among available medications requires consideration of their efficacy, mode of action, class of drugs, adverse effects and cost. If the A1C target is still not achieved after 3 months of dual therapy three drug combination is indicated. With the increasing number of available medication choices for diabetes, patients are being managed with a greater number of classes of medications in combination. Dual and triple drug combinations steadily increased from 35.0% and 6.6% in 2002 to 44.9% and 15.5% in 2013, respectively [3].

Effectiveness (HBA1c)

Most oral diabetes agents (metformin, thiazolidinediones, sulfonylureas, and GLP1 Receptor Agonists) reduce HbA1c to a similar degree by about 1 absolute percentage point when compared with baseline values. The degree of A1c reduction needed to achieve a glycemic target for an individual should be noted while choosing add-on therapy to metformin. For example, if A1c is only 0.5% above goal, one could use almost any agent and DPP4-inhibitors and SGLT2-

inhibitors would remain effective options. On the other hand, if A1c is >1% above goal, stronger agents such as GLP-1 RA, TZDs, SUs, or even insulin should be considered.

Second generation sulfonylureas (i.e. glyburide and glipizide) have comparable efficacy [4], as do various TZDs like pioglitazone and rosiglitazone [5]. When choosing from medications within the same class, other adverse effects and comorbidities should be considered. Of the second generation SUs, glipizide may be a better option than glyburide due to its shorter duration of action, particularly in patients who may be at higher risk for complications from hypoglycemia, such as the elderly [6]. There is no significant difference in A1c reduction between various DPP4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin [7]).

As a new class of drugs, sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [8] which activate the proximal nephron to decrease glucose absorption, independent of insulin and therefore can be used in any stage of type 2 diabetes. Several systematic reviews have shown that SGLT2 inhibitors are effective for controlling HbA1c [9-15]. The three most representative drugs family iSGLT2 are: Dapagliflozin, canagliflozin and empagliflozin. Recently, three new SGLT2 inhibiting drugs (ipragliflozin, tofogliflozin and luseogliflozin) were introduced to clinical practice [16-18].

Dapagliflozin was the first SGLT2 inhibitor and has many published data from clinical trials. In phase 3 trials comparing placebo for 24 weeks and dapagliflozin (2.5, 5 and 10 mg once daily) used alone or added to metformin [19], pioglitazone [20] or glimepiride [21] shown reduction of HbA1c and fasting plasma glucose in patients with T2DM . Canagliflozin was the first of this family of drugs approved by the FDA and began its commercialization in March 2013 for use in T2DM. It is an effective drug in monotherapy and has shown durable glycemic control over a two year period when compared to glimepiride [22]. At 52 weeks, canagliflozin 300mg was superior to glimepiride in A1c reduction, and at 2 years, the effect was maintained (A1c -0.74% for canagliflozin 300mg and -0.55% for glimepiride) [23]. Dapagliflozin, another member of the SGLT-2i class, has been compared to glipizide in a 4 year head-to-trial revealed no significant lowering of A1c [24]. The available data suggest that SGLT2i agents are more durable than SUs. Similar to the GLP-1 RA agents, the durable nature of SGLT-2is is likely multifactorial including weight loss, improvements in insulin sensitivity, improved beta cell function, and reduction of glucose toxicity [25,26].

The GRADE study (Glycemic Reduction Approaches in Diabetes) will compare sitagliptin, glimepiride, glargine, and liraglutide head-to-head to establish the long-term efficacy of these medications over roughly a 5 year period. The primary outcome will be time to "failure" defined as an HbA1c>7%. The trial is expected to be completed in 2020 and will give us insight into the relative long-term efficacy of these four medications.

Cost

Cost of therapy should be considered while choosing the pharmacotherapy. This will certainly help in good compliance to treatment.

Adverse effects

Adverse effects with diabetes medications are an important consideration when choosing the right medication for patients. Of the various adverse effects, hypoglycemia is the commonest and dangerous one encountered in our daily practice. The most relevant, serious, and/or common side effects of the specific drugs are discussed below.

Biguanides

Metformin which belongs to the class of biguanides is a well-tolerated drug. Though lactic acidosis is a potential adverse effect studies show that the incidence is extremely low and when it occurs, it is difficult to establish a causal relationship [12]. As per ADA and recent new FDA/EMA guideline [27,28] full dose metformin (up to 2 grams daily) can be prescribed if eGFR (mL/min per 1.73 m^2) is more than 45. It should not be given when eGFR is less than 45. If metformin is used in patients with an eGFR <60, renal function should be monitored more closely (i.e. every 3 months or sooner) and metformin should be discontinued if there is a rapid decline in renal function. Common adverse effect associated with metformin is GI intolerance including nausea, abdominal discomfort and diarrhoea. These effects are usually mild and wane with time [29]. GI symptoms can be minimized by starting with a low dose of metformin and increasing slowly. If a patient continues to have GI symptoms, extended release metformin can be considered. In summary, all patients with type 2 diabetes should be treated with metformin as first-line therapy. Long-term use of metformin may be associated with vitamin B12 deficiency. Therefore periodic measurement of vitamin B12 levels should also be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy along with periodic serum creatinine level.

Sulfonylureas (SU)

The 1st generation of sulfonylureas are obsolete .Second-generation agents are Glipizide, glyburide, glibenclamide, glimepiride, gliclazide, glyclopyramide. Sulphonylureas are effective anti-hyperglycaemic agents that reduce HbA1C by greater than 1% in monotherapy regimens. These are the main classes of drugs used in developing countries where most patients cannot afford the use of expensive newer classes of drugs. The UKPDS demonstrated the effectiveness of SU over a 10-year period. In this study, the intensive group achieved an HbA1C of 7% with a 25% reduction in microvascular complications and 10% reduction in any diabetes-related death. However, no beneficial effects on macrovascular complications were noted. The ADVANCE (Action in Diabetes and Vascular Disease) trial using Gliclazide has demonstrated in over 10,000 patients with type 2 diabetes, that an intensive strategy with conventional agents can achieve mean A1C levels of 6.5% safely with no increase in mortality and has no significant effect in reducing macrovascular disease, but reduces diabetic nephropathy by 20% [30].

Sulfonylureas are associated with hypoglycemia and weight gain (UKPDS). Therefore it is not recommended in elderly population where the risks of hypoglycemia is high leading to increased risk of myocardial infarction, stroke and falls etc. [31]. In patients with significant obesity and insulin resistance this group of agents are not preferred and needs using medications that are weight neutral or associated with weight loss. Major adverse effects associated with SUs make them a less attractive option as noted above. First-generation SUs, namely, tolbutamide and chlorpropamide, are not currently used

and were replaced by second generation SUs, including glibenclamide, glipizide, gliclazide, and glimepiride having lesser adverse effects.

However, these medications remain efficacious and cost-effective and therefore should be considered for these reasons when appropriate.

Thiazolidinediones (TZDs)

Pioglitazone is the commonly used drug that belong to this group. TZDs are the potential 2nd and 3rd line drugs and are associated with an increased risk of oedema and congestive heart failure (CHF) [32]. Weight gain associated with TZDs may be associated with oedema in part, but is likely multifactorial, including increased fat mass [33]. Results of studies looking at cardiovascular effects of TZDs are conflicting. Results from the PROactive study showed that pioglitazone reduced non-fatal myocardial infarction and stroke in patients with type 2 diabetes mellitus (T2DM) who are at high risk for cardiovascular (CV) events [34]. Whereas the RECORD study showed an increased risk of heart failure, inconclusive results on the effects on MI, but no overall increased risk of CV morbidity and mortality with rosiglitazone [35]. These medications should be used with caution in patients with CHF or other cardiac disease. TZDs have also been associated with an increased risk of osteoporotic fracture particularly in women over 65 yrs and appear to be more likely non-vertebral [36,37]. Given the variety of available classes of medications, some of which may have beneficial effects on weight and the cardiovascular system, the use of TZDs in patients with heart failure should be avoided. Though the risks of other serious adverse effects are low, the side effect profile of TZDs makes them a less desirable choice for oral medications. One should not use these medications in patients with osteoporosis, CV disease or CHF, or significant oedema.

DPP-4 Inhibitors

Drugs belonging to this class are vildagliptin, saxagliptin, teneligliptin , linagliptin and alogliptin. DPP4-inhibitors are some of the most well-tolerated classes of the anti-diabetic medications. Cardiovascular outcome trials with DPP4-i, including SAVOR-TIMI (saxagliptin versus placebo) [38], EXAMINE (alogliptin versus placebo) [39], and TECOS (sitagliptin versus placebo) [40] have shown no difference in CV endpoints with DPP4-i compared to placebo. However, in the SAVOR-TIMI trial, there were statistically significant higher rates of hospitalization for heart failure in the saxagliptin group compared to placebo [41]. In the EXAMINE trial, more patients experienced hospitalization for heart failure in the alogliptin group (106/2701, 3.9%) versus placebo (89/2679, 3.3%) [42]. These group of drugs are also associated with arthralgias [43] and the FDA has listed a post-marketing warning for joint pain associated with these medications.

GLP1 RA

Exenatide, Liraglutide and Lixisenatide are the drugs belonging to this class.Nausea is by far the most common adverse effect associated with GLP-1 RAs and it usually wanes over time [44] and can be limited by gradual dose escalation [45] except exenatide ER which is prescribed in a single dose of 2 mg weekly. These medications should not be used in patients with gastroparesis or other causes of severe chronic nausea at baseline. GLP-1 RA are contraindicated in patients with medullary thyroid carcinoma (MTC), family history of thyroid carcinoma, or patients with Multiple Endocrine Neoplasia 2 (MEN2)

due to an increase in thyroid C-cell tumors seen in rodent studies. Similar results have not been seen in human studies and may be due to species-specific differences in GLP-1 receptor expression in the thyroid [46]. Exenatide is contraindicated in patients with creatinine clearance <30 mL/min. The remaining GLP1-RA have not been well-studied in patients with eGFR <30 and are not recommended in patients with stage 4 CKD with eGFR <30 mL/min per 1.73 m^2. Lixisenatide (trade name Lyxumia in Europe and Adlyxin in U.S.) is a once-daily injectable GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus. Use with insulin or sulfonylurea may cause hypoglycemia. Dulaglutide Indicated as once-weekly SC injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.Initial dose is 0.75 mg SC once weekly and may be increased to 1.5 mg once weekly for additional glycemic control. No dose adjustment is required in renal impairment. However it is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.

Meglitinide Analogues

Meglitinide analogues (Repaglinide, Nateglinide) are a class of oral antidiabetic agents that increase insulin secretion in the pancreas. Two analogues are currently available for clinical use: repaglinide and nateglinide. In the eleven studies comparing meglitinides to placebo both repaglinide and nateglinide resulted in a reductions in glycosylated haemoglobin (0.1% to 2.1% reduction in HbA1c for repaglinide; 0.2% to 0.6% for nateglinide) [47]. Weight gain and hypoglycaemia are the potential adverse effects though it is less than for those on sulfonylureas. Meglitinides may offer an alternative oral hypoglycaemic agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated. However, there is no evidence available to indicate what effect meglitinides will have on important longterm outcomes, particularly mortality. Since there is flexibility in meal time dosing and irregular meal patterns it is a preferred 'Ramzan Drug'.

Alpha Glucosidase Inhibitors

Alpha glucosidase inhibitors (acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes. AGIs delay the absorption of carbohydrates from the small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels. The disadvantages are abdominal distension and not to be prescribed in inflammatory bowel disease, such as ulcerative colitis or crohn's disease and intestinal obstruction.

SGLT-2 Inhibitors

These are a class of medications that inhibit reabsorption of glucose in the kidney and therefore lower blood glucose. Apart from glycemic control, gliflozins have been shown to provide significant cardiovascular benefit in T2DM patients. The drugs belonging to this class are Dapagliflozin, canagliflozin, empagliflozin and many more are under the pipeline.SGLT2-i are associated with an increased risk of genital mycotic infections [48-50]. FDA issued a warning after 19 reported cases of severe urosepsis and pyelonephritis. A more serious, although rare, complication associated with SGLT2-i is ketoacidosis. Blood pressure reduction and dehydration can occur due to osmotic diuresis with SGLT2-i [51]. While this could potentially be a benefit for some patients, one should use these medications with caution in patients who may be at risk for hypotension. In patients on loop

diuretics, consider a decrease in dosage or discontinuation. Lastly, there has also been some concern about malignancy associated with the use of SGLT2-inhibitors. Dapagliflozin has been associated with an increased risk of bladder cancer and is therefore contraindicated in patients with active bladder cancer.

Patient's preference/compliance

Unfortunately the proportion of patients reaching A1c goals has remained around 50% during the last decade despite the availability of new medications [52]. This disparity is probably due to patient compliance and adherence. Poor patient compliance is multifactorial. A recent review article by Polonsky and Henry proposed that the reasons come down to six factors [53]. Those are perceived efficacy, episodes of hypoglycaemia ,treatment complexity, medication cost and trust on physician. While many of these factors are self-explanatory, one must keep in mind that perceived efficacy might be different between patient and provider. While a provider may focus on A1c reduction, a patient may prioritize weight. If a patient perceives a medication as more effective in whatever area they deem most meaningful, they are more likely to continue the drug. Finally, treatment complexity deserves special attention as taking a pill once a day results in compliance rates of roughly 80%, while that number falls to less than 50% for three times daily [54,55]. Therefore patients preference is of paramount importance in choosing the drugs [56-63].

Intermediate outcomes: overview of weight results

The effects on lipid levels varied across medication type, but most were small to moderate around 5 to 10 mg/dL in low-density lipoproteins (LDL), 10 to 30 mg/dl in triglycerides (TG), and 3 to 5 mg/dl in high-density lipoproteins (HDL). Metformin had favorable effects on all the lipid classes. Decisions regarding medications that may adversely affect lipids are important because of the importance of cardiovascular disease risk reduction in patients with diabetes.

Cardio-protectiveness

Review of various trials have concluded that favourable glycaemic efficacy does not necessarily translate to favourable cardiovascular outcomes. Cardiovascular safety needs to be prioritized over glucocentricity. This paradigm shift from glucocentricity to cardio-protectiveness poses a challenge to the practitioners to balance between the benefit of glycaemic control and the inherent risk in glucose lowering medications. As the diabetic patients are at high risk for cardiovascular morbidity and mortality the knowledge of cardioprotective effects of diabetic drugs is important for the clinicians dealing with this condition and translating it in patient care. Recommendation Based on current evidence, metformin should remain the first line drug of choice in T2DM, being the most extensively studied and demonstrating excellent cardiovascular safety even with long term use. Although evidence for the cardiovascular safety of sulfonylureas are inconsistent, the first-generation agents are probably associated with net harm and should be avoided. Newer generation sulfonylureas have a comparatively better cardiovascular profile, but weight gain remains a problem. Targeting mainly postprandial hyperglycaemia, alpha-glucosidase inhibitors favourably affect several cardiovascular risk factors, such as obesity, hypertension and high glycaemic variability with little to no risk for hypoglycaemia. The Study To Prevent Non-insulin-dependent Diabetes Mellitus (STOP-NIDDM) trial an international multicenter placebo-controlled trial has demonstrated that the use of Acarbose helps in the prevention

of cardiovascular disease in subjects with IGT mpaired glucose tolerance and T2DM.

Among the TZDs pioglitazone may have beneficial cardiovascular effects but contraindicated in heart failure. The incretin-based drugs have been at the forefront in the era of cardiovascular safety trials and have been extensively studied. Current evidence suggests that the gliptins have neutral cardiovascular effect, but may increase risk of heart failure, particularly saxagliptin. Among the GLP-1 agonists, liraglutide may have beneficial effects on cardiovascular outcomes, but this requires further validation. Similarly, the SGLT-2 inhibitors have shown promising results with empagliflozin and may potentially confer cardiovascular benefits, although additional data is needed to substantiate this. Several large ongoing randomized trials whose results are expected in the coming years. This will definitely guide the clinicians to optimize the treatment for their diabetic patients (Table 1) [64-67].

Parameters	Biguanides-Metformin	Sulfonylureas	Thiazolidinediones	DPP4 inhibitors	SGLT2 inhibitors	GLP1 receptor agonist	Alpha glucosidase inhibitors
Efficacy-Reduction of A1C	High 1-2%	High 1-2%	High 0.5-1.4%	Intermediate 0.5-0.8%	High	High 0.5-1.5%	Intermediate
Risk of Hypoglycemia	Low	Moderate	Low	Low	Low	Low	Low
Adverse Effects	GI Intolerance	Hypoglycemia	Edema , Heart Failure	Rare	Genito urinary infection	Rare	Abdominal distension
Weight gain	Loss	Gain	Gain	Neutral	Loss	Loss	Loss
Cost	Low	Low	Low	High	High	High	Low
Cardio-protecveness	CV Protective	1st generation - harmful Inconsistent	Inconsistent	No difference in CV Endpoints	CV protective	CV Protective	CV Protective

Table 1: Guides to choose the best oral diabetic agent depending on the criteria.

Conclusion

The ultimate goal is to achieve glycemic control with minimal side effects. Achieving this goal for each individual patient is of para-amount importance rather that establishing a universally accepted algorithm. Upon diagnosis, patients should be educated on appropriate lifestyle modifications primarily diet and activity. Metformin is the first line medication unless contra indicated. The advantages and disadvantages of each class of agents help the practitioners to choose the best options when combination therapy is needed. The factors considered are efficacy (A1c reduction), risk of hypoglycaemia , effect on weight and other adverse effects, cost, availability, comorbidities and frequency of administration. Patient's preference will definitely improve the adherence and compliance to drugs. Therefore a patient-centered approach is of equal importance while choosing the pharmacological agents.

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