



Review Article

Pharmacological trends in the treatment of Diabetes type 2 - New classes of antidiabetic drugs

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How to cite this article: Silvia Mihailova, Antoaneta Tsvetkova, Anna Todorova. Pharmacological trends in the treatment of Diabetes type 2 - New classes of antidiabetic drugs. IAIM, 2015; 2(4): 223-228.

Available online at www.iaimjournal.com

Received on: 20-03-2015

Accepted on: 30-03-2015

Abstract

Diabetes type 2 is a metabolic condition with significant social implications. The prevalence of type 2 diabetes is constantly increasing worldwide. Regardless of the integrated approach to the disease treatment, the proportion of patients with poor glycemic control remains high. New pharmaceutical products with improved tolerability and efficacy are in the focus of continuous research and development efforts.

Key words

Diabetes, Pharmacological trends, Antidiabetic drugs.

Prevalence and characteristics of type 2 Diabetes

Type 2 Diabetes is a chronic condition characterized by insulin resistance and/or pancreatic beta-cell dysfunction leading to decreased insulin secretion and sensitivity. As a result, people with diabetes have blood glucose levels significantly higher than normal. Over time, hyperglycemia causes deterioration in insulin resistance and progression of beta cell dysfunction. Diabetes mellitus is associated not

only with hyperglycemia but also with abnormalities in carbohydrate, fat and protein metabolism, accompanied by related specific cardiovascular and neurological complications.

Diabetes mellitus is a major socio-economic burden. In Europe, diabetes was estimated to affect 53 million of people aged between 20 and 79 at the end of 2011. Projections suggest that until 2030 the number of people with diabetes is likely to exceed 64 million in Europe and 553



million on a global scale. Type 2 diabetes accounts for not less than 85% to 95% of all diabetes [1].

Data provided by the PhRMA (Pharmaceutical Research and Manufacturers of America) show that some 25.8 million people in the USA (nearly 8.3% of country's total population) have diabetes, and 79 million people have prediabetes. As many as 1 in 3 U.S. adults could have diabetes by 2050 if current trends continue. There are several factors contributing to the increased number of newly registered diabetes cases.

- Increasing and aging population
- Changing patterns in lifestyle /sedentary lifestyle and obesity
- Improved diagnostics

Diabetes mellitus imposes a huge economic burden on the contemporary society. The health expenditures on diabetes are constantly rising. People with diabetes have medical expenditures approximately 2.3 times higher than what expenditures would be in the absence of diabetes. According to pharmaceutical industry data, the total costs of diabetes in the USA have risen to \$174 billion.

In the early nineties of the 20th century, the following blood glucose lowering pharmacotherapies in type 2 diabetes were available – biguanidines, sulfonylureas, alpha-glucosidase inhibitors and insulin.

Two decades later, incretin-based therapies evolved, including glucagon-like peptide-1 receptor agonists (GLP-1) such as liraglutide and exenatide (including forms for once-weekly administration), and various dipeptidyl peptidases 4 (DPP4) inhibitors, such as vildagliptin and linagliptin [2].

In December 2012, the first product from the group of SGLT2 inhibitors – Dapagliflozine was registered in Europe.

Since 1990, FDA has registered six new classes of drugs for the treatment of Diabetes type 2.

- Thiazolidinediones
- Meglitinides
- GLP-1 agonists
- DPP-4 inhibitors
- Dopamine agonists
- SGLT2 inhibitors

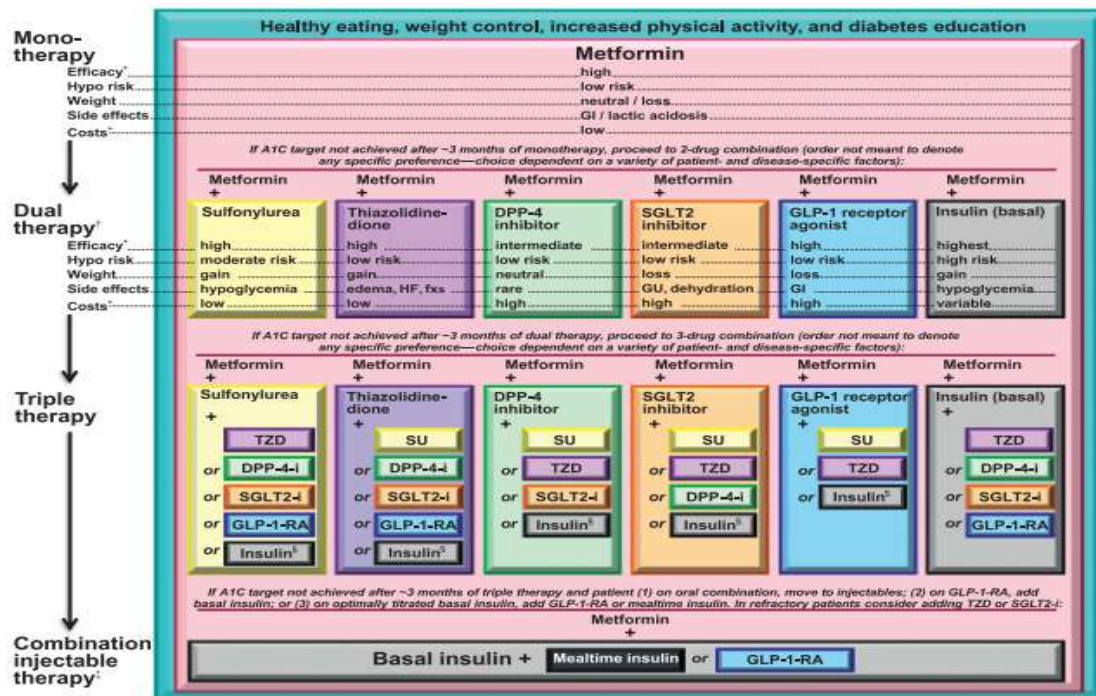
Global tendencies and International Guidelines are as per **Table – 1**. [3]

Metformin - the first-line treatment for type 2 Diabetes

Metformin inhibits hepatic and renal gluconeogenesis, and increases the sensitivity of insulin receptors. It improves glucose tolerance in patients with diabetes and increases peripheral glucose uptake and utilization. Metformin is not designed to stimulate the beta cells in the pancreas to release more insulin. It inhibits the gastrointestinal glucose absorption and has anorectic effects. Metformin can be used in combination with other medications.

Metformin does not cause hypoglycemia and weight gain and is therefore especially suitable for overweight patients with type 2 diabetes. Metformin also has beneficial effects on cholesterol and lipid levels and may help protect the heart. Some studies have indicated that it significantly reduces the risk for heart attack and death from heart disease. It is also the first-line treatment for children who need oral medications and is helpful for women with polycystic ovary syndrome and insulin resistance.

Table – 1: 2015 Basic guidelines for the treatment of type 2 diabetes provided by the American Diabetes Association /ADA/ and the European Association for the Study of Diabetes /EASD/ (5)



The recommendation that metformin be used as a first-line treatment for the majority of diabetic patients is based on its effectiveness in lowering blood glucose levels, its relatively few side effects, its long-term administration safety record, its negligible risks of hypoglycemia and its lack of causing weight gain. The evidenced cardiovascular benefits in overweight patients are also indicated as a reason to select metformin as first-line treatment [4].

Which factors necessitate the development of new classes of antidiabetic medicinal products?

According to data provided by Pharmaceutical Research and Manufacturers of America (PhRMA, www.pharma.org), US biopharmaceutical companies are currently developing 221 new drugs for the treatment of diabetes and related conditions. These products include 32 drugs for the treatment of type 1 diabetes (DT1), 130 drugs for the treatment of

type 2 diabetes (DT2), 64 for diabetes-related conditions, and 14 for unspecified conditions [5].

Diabetes treatment implies more than simply reducing blood glucose levels. The requirement that antidiabetic drugs reduce the blood glucose level is not the sole indicator for assessing drug benefits. Some 65% of patients with diabetes mellitus die of cardiovascular complications. Therefore, oral antidiabetic drugs are designed not only to reduce blood glucose levels, but ideally, to prevent cardiovascular complications and conditions, too.

The widening range of pharmacological agents for diabetes treatment increases the complexity of glycemic management and raises concern regarding the potential adverse side effects and the necessity of good glycemic control. The prospects of avoiding and reducing potential adverse effects also motivate the development of new classes of drugs.



Table - 2 and **Table - 3** below show the different classes of drugs used for the treatment of type 2 diabetes. Indicated in the table are the glycemic effects of drugs in terms of their efficacy, i.e. drugs' potential to reduce blood glucose levels and drug-induced risks of hypoglycemia. The tables include information on how drugs affect the cardiovascular system, the weight gain, as well as some class-specific adverse effects.

Table - 2 includes earlier developed oral antidiabetic drugs. As we can see, these drugs are characterized by high blood-glucose-lowering efficacy and low risk of hypoglycemia. The adverse drug reactions (ADRs) are associated with weight gain (a major drug-related issue for many patients with type 2 diabetes), bone fractures and gastrointestinal complications.

Table - 3 includes recently developed classes of drugs used for the treatment of type 2 diabetes. These drugs do not have the ADRs typical for the older drug classes. The use of these newly developed drugs is not associated with weight gain. Moreover, some of them can contribute to significant weight loss.

GLP-1 agonists /incretins/ are highly effective both for providing good glycemic control and reducing patients' weight.

In vitro studies on human cell lines have demonstrated that incretins stimulate β -cell differentiation and proliferation, while inhibiting cell apoptosis [6].

If these findings are validated by in vivo testing, incretin-based therapy might change the course and progression of diabetes, the essence of which is the progressively deteriorating beta-cell function.

The management of hypertension in diabetes is of utmost importance for the reduction of cardiovascular morbidity and mortality. SGLT2 inhibitors, such as dapagliflozin and canagliflozin are approved as treatments for T2DM in the United States and Europe. They not only improve glycemic parameters, but also contribute to weight reduction and low blood pressure, the latter associated with their osmotic diuretic effect.

Clinical studies of patients with type 2 Diabetes have demonstrated the efficacy of canagliflozin and dapagliflozin in improving glycemic control and reducing body weight and blood pressure [7, 8]. The ongoing clinical trials on cardiovascular effects of these drugs are expected to provide results within the next 4-5 years [9].

Conclusion

The management of type 2 Diabetes involves multiple goals, e.g. obtaining good glycemic control, preventing vascular complications, reducing cardiovascular risks, reducing the incidence and frequency of severe hypoglycemic events, preserving β -cell function, reducing patients' weight. Introduction of the innovative classes of GLP1 receptor agonists and SGLT2 inhibitors will not only improve glycemic control but will also reduce the incidence of cardiovascular events.

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Source of support: Nil**Conflict of interest:** None declared.**Table – 2:** Oral antidiabetic drugs.

Drug class	Biguanide	Sulfonylurea	Thiazolidinedione	α -glucosidase inhibitor
Glycemic effects				
Efficacy	High	High	High	Moderate
Hypoglycemic risk	Low	High	Low	Low
Non-glycemic effects				
Weight	Neutral/ Loss	Gain	Gain	Neutral
Cardiovascular	May lower MACEs	May reduce ischemic preconditioning	Neutral	May lower MACEs
Major side effects	Gastrointestinal, lactic acidosis	Hypoglycemia	Edema, heart failure, long-bone fractures	Diarrhoea, flatulence

MACEs – Major Adverse Cardiovascular Event



Table – 3: Recently developed classes of antidiabetic drugs.

Drug class	DPP-4 inhibitor	GLP-1 agonist	SGLT-2 inhibitor
Glycemic effects			
Efficacy	Moderate	High	
Hypoglycemic risk	Low	Low	Low - when not used in combination with insulin and/or sulfonylurea
Non-glycemic effects			
Weight	Neutral	Loss	Loss
Cardiovascular	Neutral	Data pending	Reducing blood pressure
Major side effects	Pancreatitis (rare)	Gastrointestinal	Genital mycotic infections