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Type 2 Diabetes Current and Future Medications: A Short Review

Jahangir MA[1], Imam SS[*1], Kazmi I[2], Muheem A[3]

[1]Department of Pharmaceutics, Glocal School of Pharmacy, Glocal University, Saharanpur, India
[2]Department of Pharmacology, Glocal School of Pharmacy, Glocal University, Saharanpur, India
[3]Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

[*]**Corresponding author:** Imam SS**,** Department of Pharmaceutics, Glocal School of Pharmacy, Glocal University, Saharanpur, India, E-mail: sarimimam@gmail.com

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Abstract

Diabetes Mellitus (DM) is a complex set of disease. It is basically a metabolic disorder in which body is unable to make enough insulin or it is not able to use insulin effectively or in some instances both. According to global report on diabetes released by World Health Organization, Geneva 422 million people suffers from diabetes in 2014. The number is expected to increase to 552 million by 2030. A number of researches are going on around the globe by pharmaceutical companies to exploit the huge market it provides. This short review covers the brief basics of DM and its classification medication. This review mainly focus on type 2 diabetes discussing the new classification of medication available in the market as well as the approved antidiabetic drugs for type 2 diabetes by USFDA after 2010 and the pipeline antidiabetic drugs under clinical trials. This short review article has been prepared reviewing data available from PubMed, National Institute of Health, USFDA, clinicaltrials.gov and other related sites.

Keywords: *Diabetes Mellitus, Type 2 diabetes, USFDA*

Introduction

Diabetes is a complex set of diseases. Most commonly people with diabetes suffers from high blood sugar/glucose which in scientific term known as hyperglycaemia. It is a metabolic disorder in which body is unable to make enough insulin or it is not able to use insulin effectively or both [1]. There are broadly two categories of diabetes- type 1 diabetes and type 2 diabetes. There is another type of diabetes namely gestational diabetes which usually develops during pregnancy. Type 1 diabetes is caused by lack of insulin due to destruction of insulin producing beta cells (Islets of Langerhans) in the pancreas [1]. Thus, it is also known as insulin dependent diabetes mellitus. Type 1 diabetes is an autoimmune disease which usually occurs in children and young adults and thus it is sometimes also referred to as Juvenile diabetes [1]. The main causes of type 1 diabetes are - autoimmune destruction of Beta cells, genetic susceptibility, environmental factors, viruses and infections.

Type 2 diabetes is the commonest form of diabetes. It is caused by a combination of factors including insulin resistance, in which the body is unable to use the insulin effectively. Type 2 diabetes develops when the body is unable to compensate for the impaired ability to use insulin by producing enough insulin. The main causes of type 2 diabetes are- genetic susceptibility, obesity and physical inactivity, insulin resistance, abnormal glucose production by the liver, beta cell dysfunction [1].

According to global report on diabetes released by World Health Organization, Geneva 422 million people suffers from diabetes in 2014 (http://www.who.int/mediacentre/factsheets/en) [2]. The number is expected to increase to 552 million by 2030 [3]. The numbers suggest that 80% of the people with DM are living in low or middle income countries [3]. A number of researches are going on around the globe by pharmaceutical companies to exploit the huge market it provides.

Conventional Medicines and Future Drugs

No cure has yet been found for the disease; however, treatment modalities include lifestyle modifications, treatment of obesity, oral hypoglycemic agents, and insulin sensitizers like metformin, a biguanide that reduces insulin resistance, is still the recommended first line medication especially for obese patients. Other effective medications include non-sulfonylurea, thiazolidinediones, alpha glucosidase inhibitor, and insulin. The classification of conventional anti-diabetic medication and their mechanism of actions (www.drugs.com) [4] are listed in Table 1. Recent research into the pathophysiology of type 2 DM has led to the introduction of new medications like glucagon-like peptide 1 analogous, dipeptidyl peptidase-IV inhibitors, inhibitors of the sodium-glucose cotransporter-2 and 11ß-hydroxysteroid dehydrogenase 1, insulin-releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, metabolic inhibitors of hepatic glucose output and quick-release bromocriptine. Inhaled insulin was licensed for use in 2006 but has been withdrawn from the market because of low patronage [3].

Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl Peptidase-4 Inhibitors (DPP-4) or in short gliptins falls in the newest class of drugs used for type 2 diabetes indications. DPP-4 is actually an enzyme which inhibits glucagon like peptide-1 or GLP-1. The function of GLP-1 is to trigger the β-cells of pancreas to release insulin. DPP-4 inhibitors stop DPP-4 enzyme from destroying GLP-1, which in turns stimulates β-cells of pancreas to release more insulin. Sitagliptin is an approved drug from FDA of this class. It is either used as a sole drug or in combination with metformin for the management of type 2 diabetes.

GLP-1 Mimetics (Incretin Mimetics)

GLP-1 is a hormone which is released from the digestive tract at the time of digestion. The function of GLP-1 is to stimulate the β-cells of pancreas to release more insulin. Since, a DPP-4 enzyme destroys GLP-1. The GLP-1 mimetic mimics the function of GLP-1 hormone and stimulates pancreas to release insulin. The GLP-1 synthetic mimetic agent is not recognized by DPP-4 enzyme as the same naturally occurring GLP-1 hormone. Exenatide is an injectable medication approved by FDA for the management of type 2 diabetes [5]. Liraglutide is another drug approved in this class.

Amylin Analog

Amylin is a hormone, which reduces glucagon. Glucagon is another hormone which causes the body to release or produce glucose. Thus, amylin analog indirectly influences the glucose level in the blood by reducing the glucagon level in the body [5]. Pramlinitide is an injectable medication approved by FDA for the management of type 2 diabetes.

Rimonabant

Endocannabinoid system (ECS) is a newly found physiological endocrine system that plays a key role in appetite and energy metabolism both in the brain as well as in the adipose tissue [6-8]. In the animal studies, it has been found that blocking ECS has led to weight loss and improved insulin sensitivity. By blocking CB1 receptors, rimonabant has been shown to reduce weight by suppressing appetite and by modifying glucose and fat metabolism [8-10]. Rimonabant has undergone

phase 3 trials and is licensed for use in patients who have a BMI >30 kg/m^2 or BMI >27 kg/m^2 with an additional risk factor such as dyslipidaemia or diabetes [11].

New Medications and Pipeline Drugs

Upon reviewing USFDA data of approved drugs for type 2 diabetes since 2010, it was found that there are about fifteen new medicines or new combination of old medicines for type 2 diabetes approved. The maximum approval of type 2 medication was for Boehringer Ingelheim with three approvals, while Eli Lilly got two USFDA approvals for type 2 diabetes indication since 2010. The list is tabulated in Table 2 [12].

There a number of new medicinal entities undergoing clinical trials and is under the pipeline of many major pharmaceutical industries. Upon short reviewing of type 2 diabetes medications in clinicaltrials.gov it was found that GlaxoSmithKline has two drugs namely Denagliptin and GSK523338 both in their phase 3 trials, AstraZeneca have Pramlintide Acetate which is in phase 4. Other medication which is in their phase 4 trials are - Cholecalciferol, and Iobitridol which belongs to Tufts Medical Center and Merck Sharp & Dohme Corp. respectively. The list is tabulated in Table 3 [13].

Conclusion

Diabetes is complex metabolic disorder, which influences the whole metabolic function of the patient. A person suffering from diabetes may also develop some other disease like hypertension, cataract, kidney dysfunction etc. The number of persons suffering from diabetes is increasing day by day and is expected to influence 552 million people in the world by 2030. Most of the people suffering from diabetes either belongs to low or middle income countries. Diabetes provides a huge market for the pharmaceutical industry. A number of new medicines have been approved by USFDA since 2010. The major pharmaceutical companies are sponsoring clinical trials and are having a number of new medicinal entities or new combination of old medicinal strategies for type 2 diabetes in their pipeline drug. But the dilemma with this disease is that no possible cure is still reported.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 1: Classification and mechanism of action of conventional anti-diabetic drug

Class of Anti-diabetic drug	Mechanism of Action	Examples
Alpha-glucosidase inhibitors	Competitive and reversible inhibition of Alpha-glucosidase enzyme	Acarbose, Miglitol
Meglitinides	Stimulates the pancreas to release insulin in response to meal	Repaglinide, Nateglinide
Non-sulfonylureas (biguanides)	Inhibits the amount of glucose produced by liver, increased insulin receptor binding, stimulates tissue uptake of glucose	Metformin
Sodium-Glucose transporter-2 (SGLT-2)	Lowers renal glucose threshold, results in increased amount of glucose excretion from urine.	Canagliflozin, Empagliflozin, Dapagliflozin
Sulfonylureas	Stimulates the pancreas to release more insulin	Chlorpropamide, glimepiride, Glyburide, Glipizide, Tolazamide, Tolbutamide
Thiazolidinediones (glitazones)	Acts as agonists for peroxisome proliferator-activated receptors gamma (PPARgamma), behaving as insulin sensitizer	Rosiglitazone, Pioglitazone
Insulin	Polypeptide hormone, regulates the amount of glucose in the blood	Insulin regular, Insulin aspart, Insulin lispro, Insulin isophane, Insulin regular, insulin glargine, Insulin detemir, Insulin zinc extended, insulin degludec

Table 2: List of drugs approved by USFDA after 2010 for type 2 diabetes

Drug	Brand Name	Company	Approved Year
Lixisenatide	Adlyxin	Sanofi Aventis	2016
Empagliflozin + Metformin Hydrochloride	Synjardy	BoehringerIngelheim	2015
Insulin Degludec Injection	Tresiba	Novo Nordisk	2015
Dapagliflozin	Farxiga	Bristol-Myers Squibb	2014
Empagliflozin	Jardiance	Boehringer Ingelheim	2014
Albiglutide	Tanzeum	GlaxoSmithKline	2014
Dulaglutide	Trulicity	Eli Lilly	2014
Dapagliflozin + Metformin Hydrochloride	Xigduo XR	AstraZeneca	2014
Canagliflozin	Invokana	Janssen Pharmaceuticals	2013
Alogliptin	Nesina	Takeda	2013
Exenatide XR for Injection Suspension	Bydureon	Amylin	2012
Linagliptin+ Metformin Hydrochloride	Jentadueto	Eli Lilly	2012
Sitagliptin And Simvastatin	Juvisync	Merck	2011
Linagliptin	Tradjenta	Boehringer Ingelheim	2011
Liraglutide	Victoza	Novo Nordisk	2010

Table 3: List of some pipeline anti-diabetic drugs under clinical trials

Drug	Sponsor	Phase
MBX-102	Cymabay Therapeutics, Inc.	Phase 3
Denagliptin (GW823093)	GlaxoSmithKline	Phase 3
Cholecalciferol	Tufts Medical Center	Phase 4
Pramlintide Acetate	AstraZeneca	Phase 4
ETC-1002	Esperion Therapeutics	Phase 2
DS-8500a	Daiichi Sankyo Co., Ltd.	Phase 2
ASP1941	Astellas Pharma Korea, Inc.	Phase 3
GSK523338	GlaxoSmithKline	Phase 3
Iobitridol	Guerbet	Phase 4
Omarigliptin	Merck Sharp & Dohme Corp.	Phase 1

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