Antipsychotic-Induced Type 1 and Type 2 Diabetes Mellitus with Special Reference to Lumateperone

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***Abstract*—Antipsychotic drugs are widely used in the management of psychiatric disorders such as schizophrenia and bipolar disorder. With the increasing use of second-generation (atypical) antipsychotics, metabolic adverse effects including weight gain, insulin resistance, dyslipidemia, and diabetes mellitus have emerged as major clinical concerns. Among these, the development of Type 2 diabetes mellitus significantly increases cardiovascular risk and overall morbidity in psychiatric patients. The mechanisms responsible for antipsychotic-induced diabetes are multifactorial and include appetite dysregulation due to histamine (H_1) and serotonin (5-HT_2C) receptor blockade, impaired insulin sensitivity, altered pancreatic β-cell function, and increased hepatic glucose production. The risk of diabetes varies among antipsychotic agents, with clozapine and olanzapine showing the highest metabolic liability. In contrast, newer antipsychotics such as lumateperone demonstrate a comparatively safer metabolic profile. This project reviews the association between antipsychotic therapy and diabetes mellitus, explains the underlying mechanisms, compares the diabetogenic potential of different antipsychotics, and highlights the clinical importance of selecting metabolically safer agents. This drug review provides a comprehensive analysis of a novel antipsychotic called lumateperone. Lumateperone gained FDA approval in 2019 for treating schizophrenia and later, in 2021, fortreating bipolar depression.**

***Index Terms*—diabetes mellitus, current anti-diabetics, novel drugs and targets, Type1 diabetic, Type 2 diabetic, psychiatric disorders, psychiatric disorders, bipolar disorder, lumateperone.**

I. INTRODUCTION

For severe mental diseases like schizophrenia and bipolar disorder, psychotropic drugs are the primary form of care. Even though these drugs are good in reducing psychotic symptoms, prolonged use of them is linked to a number of negative side effects. The influence of metabolic disorders on patient morbidity and mortality, especially diabetes mellitus, has attracted a lot of attention. Type 2 diabetes mellitus, obesity, and insulin resistance are all more probable to develop in patients using atypical antipsychotics. subsequently, secure and effective pharmacotherapy depends on an understanding of the metabolic dysfunction brought on by psychotropic drugs.

II. DIABETES MELLITUS

Diabetes mellitus (DM) has become a major worldwide healthcare concern due to its sharp increase in occurrence. DM affects people of all ages, socioeconomic backgrounds, and demographic subgroups in nearly every country on the planet. Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

1.1. Types of diabetes mellitus

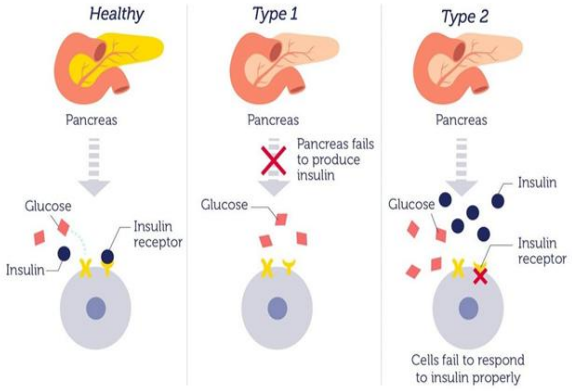

Fig.1: Types of Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM)

The complicated condition known as type 1 diabetes mellitus may be brought on by environmental factors that change immunological pathways as well as genetic risk. T1DM results from the autoimmune cell-mediated death of insulin-producing pancreatic b-cells by macrophages and CD4+ and CD8+ T-cells. Four different indicators of this pancreatic b-cell loss are as follows:

- Islet cell autoantibodies.
- Autoantibodies to Insulin.
- Autoantibodies to Glutamic Acid Decarboxylase (Gad65).
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b.

The environmental trigger and genetic factors determine the type of autoantibody reaction that appears early. Depending on whether hyperglycemia and its associated symptoms (such thirst and polyuria) are present or absent, the pathophysiology of type 1 diabetes can be split into three stages.

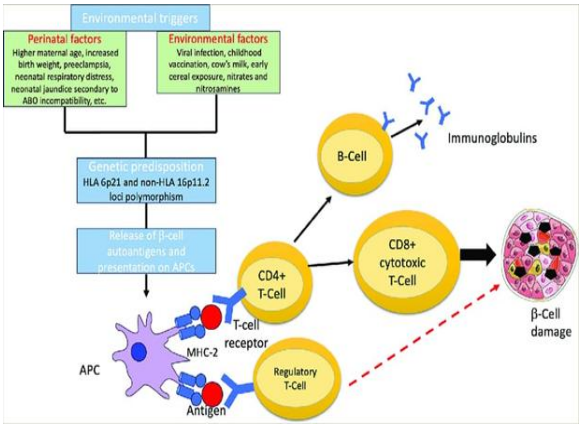

Fig 2: diagrammatic representation of Type 1 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM)

The chronic metabolic disease known as type 2 diabetes mellitus (T2DM) is typified by hyperglycemia, or elevated blood glucose. It happens when the body either produces insufficient insulin to maintain normal glucose levels or rejects the effects of insulin, a hormone that controls the flow of sugar into your cells. The way your body uses glucose, or sugar, as fuel is impacted by type 2 diabetes. If left untreated, it prevents the body from using insulin as it should, which can result in elevated blood sugar levels.

Type 2 diabetes has the potential to severely damage the body over time, particularly the blood vessels and nerves.

Diabetes type 2 is frequently avoided. Genetics, obesity, and insufficient exercise are some of the factors that lead to type 2 diabetes. Type 2 diabetes affects more than 95% of diabetics. Type 2 diabetes was once referred to as adult onset or non-insulin dependent. This kind of diabetes was only observed in adults until recently, but it is now becoming more common in kids as well.

T2DM is primarily driven by two interrelated problems:

- Release enough insulin to over Insulin Resistance: Cells in your muscles, fat, and liver become resistant to insulin. Because of this, they don't take in enough sugar.
- Betacell Dysfunction: The pancreas is unable to produce enough insulin to overcome this resistance, leading to a "relative" insulin deficiency.
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1. Insulin Resistance (IR)

Insulin resistance is the result of a decreased response to insulin by the body's target tissues, mainly the skeletal muscle, adipose (fat) tissue, and liver. In the liver, resistance results in a decreased ability to control the generation of glucose, which raise fasting blood sugar. Resistance in the muscle/fat inhibits the bloodstream's ability to absorb glucose efficiently after meals, resulting in postprandial hyperglycemia.

2. Beta-cell dysfunction in the pancreas.

This refers to the pancreatic beta-cells' inability to come the resistance that already exists. Phase of Compensation: In order to maintain normal blood sugar levels, the pancreas first makes up for insulin resistance by producing more insulin ("hyperinsulinemia")

Decompensation Phase: Genetic vulnerability and "metabolic stress" (such as oxidative stress and glucotoxicity) all combine to cause these cells to be unable to meet the increasing demand, which results in a progressive decrease in insulin secretion and the development of type 2 diabetes.

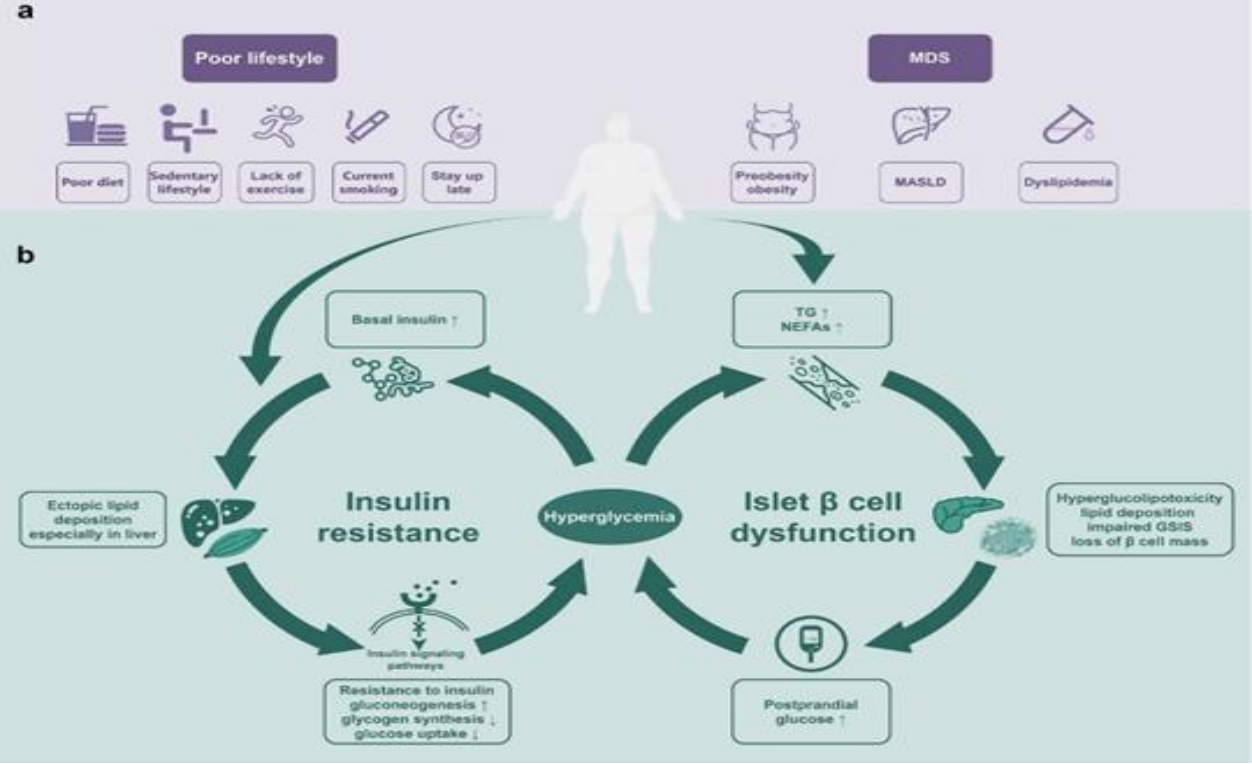

Fig.3: Type 2 Diabetes Mellitus

Difference Between Type1 and Type2 Diabetes Mellitus

Table No.1

Feature	Type1 Diabetes Mellitus	Type2 Diabetes Mellitus
Cause	Autoimmune destruction of pancreatic β-cells	Insulin resistance+ relative insulin deficiency
Insulin	Very low or absent	Normal, high, or low (but effective)
Age of onset	Usually, childhood or adolescence	Usually adulthood (>40 years), but now also in young people
Body weight	Usually normal or underweight	Often overweight obese
Onset of symptom	Sudden	Gradual
Genetic influence	Moderate	Strong
Autoantibodies	Present	Absent
Risk of ketoacidosis	Common	Rare
treatment	Lifelong insulin therapy	Lifestyle modification +oral drugs + insulin
prevention	Not preventable	Often preventable with lifestyle change

Lumateperone:

Drug Profile and its Relation with Diabetes Mellitus Introduction Lumateperone is a newer atypical antipsychotic that has gained attention due to its unique mechanism of action and improved safety profile. It is mainly used in the treatment of schizophrenia and bipolar depression. Unlike many older antipsychotic drugs, lumateperone is associated with fewer side effects, especially metabolic complications such as weight gain and diabetes. This makes it particularly important in modern pharmacotherapy.

Generic Name: Lumateperone

- Brand Name: Caplyta
- Drug Class: Atypical Antipsychotic
- Year of Approval: 2019 (FDA approved)

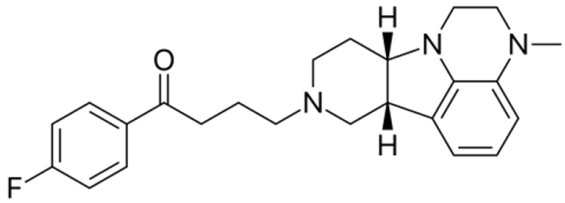

Fig.4: chemical structure of Lumateperone

Lumateperone Therapeutic Use

Lumateperone is indicated for the treatment of schizophrenia and bipolar depression (both type I and II). It may also be used as an adjunct in major depressive disorder in some cases.

Mechanism Of Action

Lumateperone has a unique 'triple mechanism' of action. It acts on dopamine, serotonin, and glutamate neurotransmitter systems. It functions as a presynaptic partial agonist and postsynaptic antagonist at dopamine D2 receptors. It is also a potent antagonist at serotonin 5-HT2A receptors and enhances glutamate signaling. This balanced activity helps in improving symptoms while reducing adverse effects.

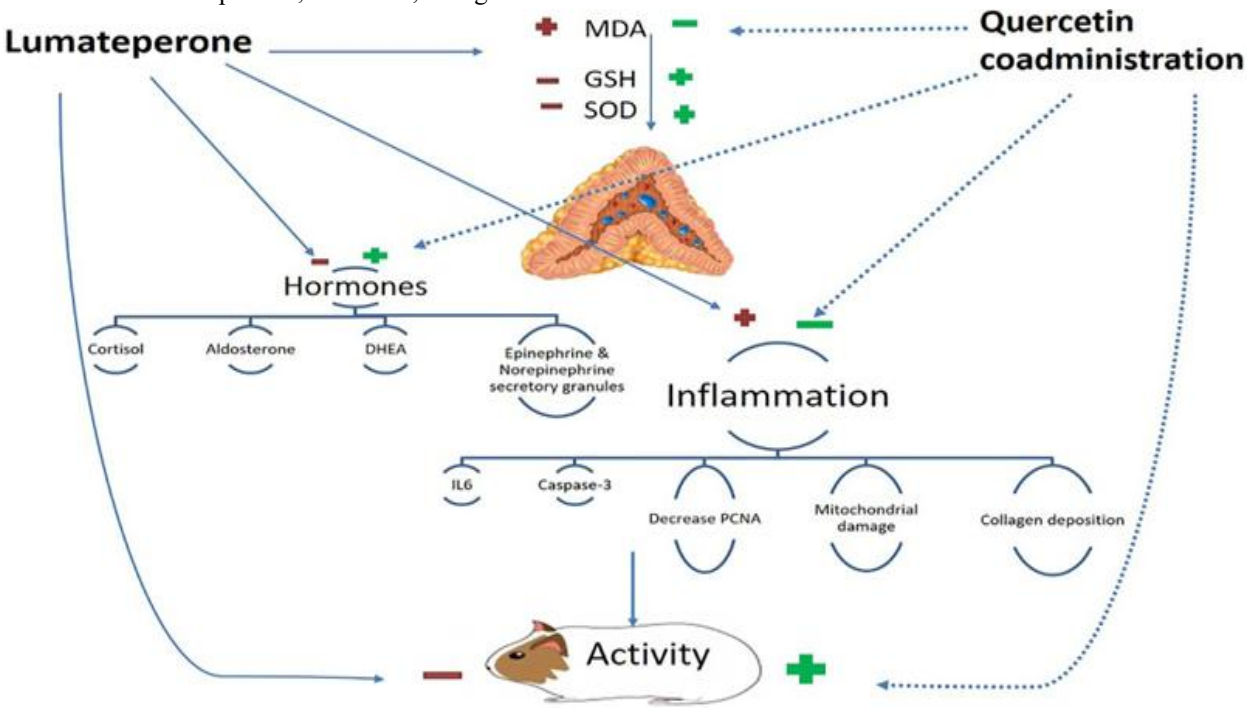

Fig.5: Mechanism of action of Lumateperone

Pharmacokinetics

Lumateperone is administered orally and has a bioavailability of around 4.4%. It reaches peak plasma concentration within 1 to 4 hours. The drug has a half-life of approximately 13 to 21 hours, allowing once-daily dosing. It is mainly metabolized by CYP3A4 enzymes and excreted via urine and feces.

Pharmacodynamics

The unique pharmacologic profile of lumateperone allows it to synergistically modulate serotonergic, dopaminergic, and glutamatergic neurotransmission.

Adverse Effects

Common side effects include

- Somnolence
- Sedation
- Fatigue
- Constipation.

Some patients may also experience

- Dizziness
- Dry Mouth
- Nausea

However, compared to other antipsychotics, lumateperone has a lower risk of extrapyramidal symptoms and hormonal disturbances.

Relation with Diabetes Mellitus

One of the major concerns with many atypical antipsychotics is their association with metabolic side effects such as weight gain, insulin resistance, and hyperglycemia, which can lead to type 2 diabetes mellitus. Drugs like olanzapine and clozapine are well known for these risks. Lumateperone, however, shows a significantly improved metabolic profile. It has minimal affinity for receptors such as histamine H1 and serotonin 5-HT2C, which are responsible for increased appetite and weight gain. Clinical studies have shown that lumateperone does not significantly increase blood glucose levels, body weight, or lipid levels. Because of this, lumateperone is considered a safer option for patients who already have diabetes or are at high risk of developing metabolic disorders. This makes it a valuable choice in long-term

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