Risk of metabolic syndrome associated with the first and second generation Antipsychotic treatment.

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Abstract: The metabolic syndrome (MetS) is a major public-health challenges worldwide. MetS is defined by different health organization as a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia. Central adiposity is a key feature of the metabolic syndrome, as reflected by the strong relationship between the prevalence of the metabolic syndrome and waist circumference (WC). The aims of this project are to review the components of metabolic syndrome and to review the literature describing the potential for antipsychotic medications to cause weight gain, hyperlipidemia and glucose dysregulation which are the components of metabolic syndrome. Antipsychotics drugs have been found to be strongly associated with weight gain, insulin resistance/glucose intolerance and dyslipidemia. Additionally, patients on antipsychotic drugs with metabolic syndrome are at high risk to develop type 2 diabetes and cardiovascular diseases. Most of the reviewed articles showed that atypical antipsychotics are with higher risk to develop metabolic syndrome than typical antipsychotics. It has been found that clozapine and olanzapine cause the highest significant changes in weight gain, glucose intolerance, dyslipidemia and their complications. Further, the risk of type 2 diabetes is higher in patient's taking atypical antipsychotics (specifically; olanzapin&clozapine) than in those taking typical drugs.

List of abbreviations:

Mets Metabolic syndrome
ATP III Adult Treatment Panel – III
IFG Impaired fasting glucose
EGIR European group insulin
WC Waist circumference
NCEP National cholesterol education adult treatment
IDF International Diabetes Foundation
FFA free fatty acid
RAS rennin angiotensin system
AT Angiotensin
GLUT glucose transporter type 1 &4
TRL triglycride rich lipoproteins
CV cardiovascular
TC total cholesterol
SCD sudden cardiac death

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1. Introduction:

1. Metabolic syndrome:

The metabolic syndrome (MetS) has become one of the major public-health challenges worldwide. Metabolic syndrome, variously known also as syndrome X, insulin resistance, etc., MetS is defined by different health organizations as a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia **(Alberti, *et al*., 2005)**. Currently, there are at least 6 different classification criteria for MetS developed by various expert panels. The selected criteria for metabolic syndrome differ from organizations to another.Therefore, the National Heart, Lung, and Blood Institute, in collaboration with the American Heart Association, arranged a conference to examine scientific issues related to definition of the MetS. The conference did not specifically recommend one criteria over another for the definition of the MetS, but it recommended the ATP III criteria to identify patients at increased risk for CVD **(Grundy *et al*., 2004**).

2. Components of metabolic syndrome:

1. Obesity:

Obesity results from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue and it was defined as a Body mass index (BMI) exceeding 30 kg/m2 according to WHO. Obesity generates a worldwide epidemic with prevalence rates which are increasing in most developed, as well as the developing world. By 2025, the global obesity prevalence will reach 18% in men and exceed 21% in women **(Kyrou*et al.*, 2018).**

Centrally accumulation of body fat is associated with insulin resistance, whereas distribution of body fat in a peripheral pattern is metabolically less important. Obesity is associated with a large decrease in life expectancy **(Atilla,2017),**andit was found to increase the risk of depression, most pronounced among Americans and for clinically diagnosed depression**(Floriana*et al*., 2010).**

2. Insulin resistance:

Insulin resistance is a condition in which the ability of target tissues (e.g., muscle, liver, fat) to respond to the normal actions of insulin is decreased. Consequently, the ability of insulin to promote glucose uptake, inhibit hepatic glucose production, and suppress lipolysis in target tissues is diminished, resulting in excess circulating glucose and hyperinsulinemia**(Bagry*et al.*, 2008).**

Most common insulin resistance mechanisms include a decrease in the number of insulin receptors and of their catalytic activity, alteration of phosphorylation state in insulin receptor and defects in GLUT-4 expression and function **(Gutiérrez-Rodelo*et al.*, 2017).**

3. Hypertension:

Concerning the mechanism for the development of hypertension in metabolic syndrome, the lack of insulin resistance in the kidney increases sodium reabsorption by hyperinsulinemia, leading to sodium retention in the body, and resultant salt-sensitive hypertension(**Fujita, 2008).**

Increased renal sodium retention in obesity was found to be associated with increases in sympathetic system and renin-angiotensin system(RAS) activation. Increased sodium retention causes a compensatory increase in fluid volume and initiates the rise in blood pressure**(Peters, 2007).** It has been recently discovered that adipocytes also produce

aldosterone in response to ATII. In this regard, the adipocyte may be considered small renin-angiotensin aldosterone system **(Kaur, 2014).**

4. Dyslipidemia:

Insulin resistance is a key factor in the pathophysiology of dyslipidemia and is associated with a characteristic pattern of lipid abnormalities. Insulin resistance leads to an atherogenic dyslipidemia in several ways. First, insulin normally suppresses lipolysis in adipocytes, so an impaired insulin signaling increases lipolysis, resulting in increased FFA levels. In the liver, FFAs serve as a substrate for the synthesis of Triglycerides (TGs). FFAs also stabilize the production of apoB, the major lipoprotein of very low density lipoprotein(VLDL)particles, resulting in a more VLDL production **(Kaur, 2014).**

2. The Aim of the study:

The aims of this project are to present an overview of the components of metabolic syndrome and to review the literature describing the potential for antipsychotic medications (both FGAs and SGAs) to cause weight gain, hyperlipidemia and glucose dysregulation which are the components of metabolic syndrome.

3. Methodology:

Review articles of selected studies on metabolic syndrome and effects of antipsychotic drugs on theparameters of metabolic syndrome. This conducted review by searching for the keywords metabolic syndrome, antipsychotic drugs, weight gain, hyperlipidemia and glucose dysregulationusing different scientific web-sites including scholar Google, science direct, PubMed and midline, limiting the search to English language articles, full text.

4. Data and results:

Antipsychotics are a heterogeneous group of substances used primarily to treat schizophrenia, mania, delusions, and states of agitation, they are classified according to its chemically structure into two types typical Antipsychotics, or First Generation or traditional Antipsychotic Drugs and Atypical Antipsychotics, or Second Generation Antipsychotic Drugs **(Katzung,2018).**

Antipsychotics and Obesity:

It has been reported in many articles and reviews that antipsychotics can cause metabolic problems.Weight gain is one of the metabolic syndrome components that can be induced by antipsychotics. According to **Baptista (1999),** long-term administration of typical(first generation) and atypical antipsychotic(second generation) drugs induces excessive weight gain.

Interest in antipsychotics causing weight gain was awakened after the innovative study by **Allison *et al*., (1999),** which was the first meta-analysis on the subject. The study evaluated weight gaindue to both first- and second-generation antipsychotics (FGAs and SGAs, respectively) at standard doses for 10 weeks. It showed that patients on placebo appear to have lost weight and those on antipsychotics were associated with weight gain. There is, considerable variability in weight gain among the various FGAs and SGAs. The antipsychotics; clozapine, olanzapine, thioridazine, sertindole, chlorpromazine and risperidone were all reported to cause significant weight gain varying from 4.45 to 2.10 kg(**Figure1**). However, ziprazidone, haloperidol and malindone does not cause significant change in weight gain **(Allison *et al*., 1999).**

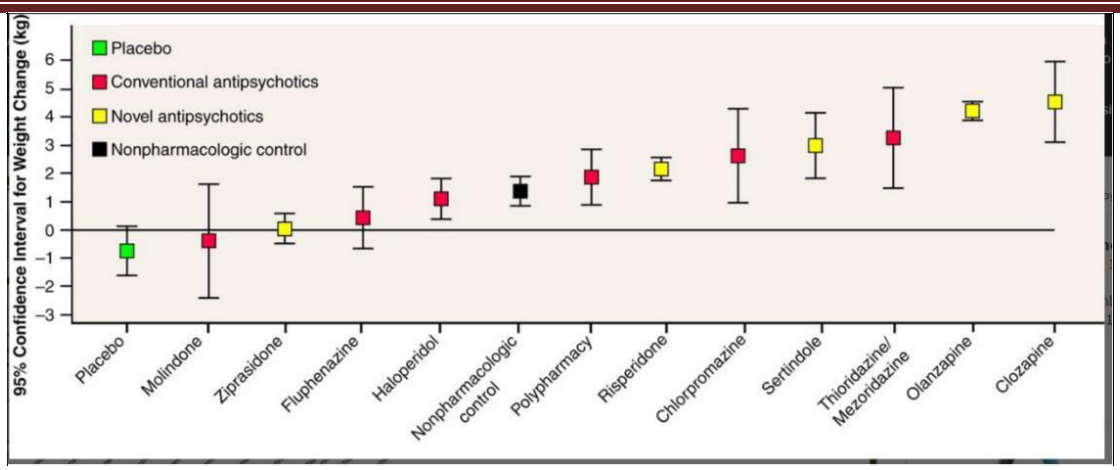

Figure 1: 95% Confidence Intervals' for Weight Change after 10 Weeks on Standard Drug Doses adapted from *(*Allison *et al*, 1999).

A year later **Green *et al*.,(2000)** state that chronic use of antipsychotic drugs are frequently associated with often-substantial weight gain that is a special concern with the atypical antipsychotics (second generation).

A study done by **Covell*et al.,* (2004)**on 227 long-stay patients in hospitals, 138 of them were on first generation antipsychotics and 89 were switched to clozapine. The study examinedpercentage of body weight gained during 2 years for patients. Patients who switched to clozapine gained a greater percentage of weight (13 pounds, 7%) than did patients remaining on first generation medications (5 pounds, 4%) at the end of 2 years(24months)(**Figure2**). However, Patients gained weight whether they switched to clozapine or remained on first generation antipsychotic medications, but weight gain was significantly greater in the clozapine-treated group.

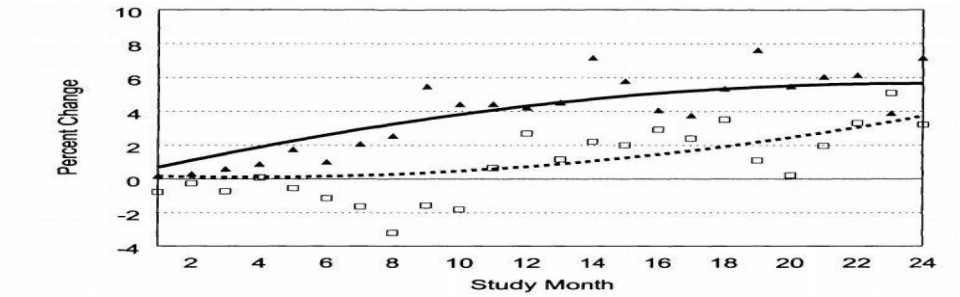

Figure 2: percentage of weight gained over based line (▲: switched to clozapine; □: first generation antipsychotics) *(Covell, et al., 2004).*

Another study done by **(Rummel-Kluge *et al*.,2010)** using meta-analysis reported that olanzapine and clozapine produced more weight gain than all other second-generation antipsychotics, Clozapine produced statistically significant more weight gain than risperidone (5.3 lb, 2.4 kg). Olanzapine produced significantly more weight gain than amisulpride (7.3lb, 3.31 kg), aripiprazole (7.7lb, 3.49 kg), quetiapine (4.2lb, 1.9 kg), risperidone (4.6lb, 2.08 kg) and ziprasidone (3.82 kg). Risperidone produced significantly more weight gain than amisulpride (2.7lb, 1.22 kg). Sertindole produced significantly more weight gain than ziprazidone (6.3lb, 2.85 kg).

Antipsychotics are different in their risk of causing weight gain. The fastest weight gain occurs in the first 6 months after starting an antipsychotic. Weight gain can continue after this

but more slowly, which suggest a duration dependent relation. Two meta-analysis studies, one by **(Parsons *et al.,* 2009)** and another by **(Tarriconee*t al.,* 2010),** which compare the weight gained through short and long periods of Antipsychotics exposure. Both studies showed that long term use of Antipsychotics was associated with more weight gain compared with short term use. Antipsychotic drugs may interfere with feeding behaviors and energy balance, processes that control metabolic regulation. Reward and energy balance centers in central nervous system constitute the central level of metabolic regulation**(Siafis et al., 2018)**.

Antipsychotics and dyslipidemia:

Lipid abnormalities have been thought to occur in patients treated with typical and atypical antipsychotics. These abnormalities are largely associated to weight gain. Therefore, agents associated with the greatest weight gain may have a greater tendency to cause dyslipidemia.

The first double-blind trial by **Clark *et al.,* (1972)**, applied on schizophrenic in patients treated with loxapine, chlorpromazine or placebo.It has been found that there is a significant increase in serum cholesterol and Triglycerides concentrations in the chlorpromazine and loxapine treatment groups compared to placebo.

A cross sectional analysis by **Sasaki *et al.,* (1984)** found that patients chronically treated with phenothiazine(e.g. chlorpromazine) for long periods, had HDL-c levels significantly lower than normal controls serum. Triglycerides level was significantly higher in patients treated with phenothiazines than in controls.

Additionally, **Shafique, *et al.,* (1988)**, demonstrated that Triglycerides, VLDL-c and LDL-c levels were significantly elevated in patients on phenothiazines and LDL-c in patients on butyrophenone; VLDL-c and LDL- c levels were significantly higher and HDL-c levels lower in patients on combined therapy (**Table 1**).

Table 1: Cholesterol levels in patients and control treated with tranquilizers (*Shafique, et al., 1988*).

Groups	VLDL(mg/dl)	LDL(mg/dl)	HDL(mg/dl)
Controls	24.7±15.8	121.5±19.7	66.2±15.7
Phenothiazine	33.4±17.5 *	137.3±31.7 * *	62.6±14.3
Butyrophenone	31.7±16.3	135.9±29.5 *	61.4±13.9
Mixed therapy	37.1±19.2 * *	142.6±32.5 * * *	57.5±12.6 *
The difference is statistically significant, *p<0.05, * *p<0.02, * * *p<0.01 as compared to controls			

In 1996, few years after introduction of atypical antipsychotics to the market, **Ghaeli&Dufresne, (1996)**found that serum TG were significantly higher in clozapine group in compare to typical antipsychotics group.
Furthermore, **Koro*et al*., 2002**stated that olanzapine use was associated with nearly a fivefold increase in the probabilities of developing hyperlipidemia compared with no antipsychotic exposure and more than a threefold increase compared with those receiving conventional agents.

Retrospective comparison study by **Wirshing*et al.,* (2002),** compare total cholesterol (TC) and triglycerides (TG) in patients on clozapine; olanzapine; risperidone; quetiapine and haloperidol.The results showed that clozapine and olanzapine associated with greatest increase in TC and TG, levels while risperidone were associated with a decrease.**Goodnick,**

and Jerry, (2002), meta-analysis of short-term trial data showed that Total Cholesterol(TC) levels following aripiprazole administration were lower than for haloperidol, risperidone or placebo; in a long period trial comparing aripiprazole to olanzapine found significant differences after 4 weeks; olanzapine increased total cholesterol, whereas aripiprazole cause non-significant increases in total cholesterol. Treatment with clozapine, risperidone, quetiapine, olanzapine, ziprasidone, and the first generation antipsychotic medications, but not aripiprazole, was associated with a significantly greater risk of new-onset hyperlipidemia than treatment without an antipsychotic medication **(Olfson*et al.*, 2006).**

Roohafza*et al.*, (2013) compare lipid profile in typical and atypical group which shows a higher mean in TC, LDL, and Apo B in the conventional group than the atypical group, with a significant difference in TC (P = 0.001), LDL (P = 0.001), and Apo B (P = 0.001)(**Table 2**).

Table 2: lipid profile in two antipsychotics group adapted from (Roohafza*et al., 2013*).

	Conventional group(n=64)	**Atypical groups (n=64)**	**P**
Total Cholesterol(Mean±SD)mg/dl	249.75±34.44	214.25±50.32	0.001
LDL (Mean±SD)mg/dl	149.96±24.21	131.93±36.81	0.001
HDL (Mean±SD)mg/dl	44.71±11.81	45.18±29.5	0.800
Apolipoprotein A Mean±SD)mg/dl	137.12±23.69	134.05±22.71	0.450
Apolipoprotein B Mean±SD)mg/dl	122.81±20.51	104.56±33.63	0.001

Insulin resistance associated with antipsychotics treatment:

- **Impaired glucose homeostasis :**

Data from most studies suggest that the prevalence of glucose deregulation in schizophrenic patients is almost 2 times greater than the prevalence reported in the general population. Additionally, Probability of developing type II diabetes mellitus (DM) would also be higher in patients diagnosed with schizophrenia **(Lindenmayer*et al.*, 2003).**

Also, **Hennemanet *al*., (1954),** noted increased incidence of abnormalities in glucose metabolism in people with schizophrenia prior the introduction of antipsychotic medications. As it was believed that changes in neurotransmission within CNS regions such as, the hypothalamus in schizophrenia may also affect the metabolic signaling in the periphery including the endocrine pancreas, liver, and adipose tissue. This believes support that, Antipsychotics may also aggravate the preexisting metabolic problems in people with schizophrenia as they may further alter metabolism through their effect on neurotransmission within CNS regions **(Freyberg *et al*., 2017).**

However, **Arranz*et al*., (2004)** demonstrated that reduced sensitivity to insulin and hyperinsulinemia found in schizophrenic patients are not related to the diagnosis itself, but to previous use of antipsychotics. As showing the existence of insulin resistance before development of type II diabetes mellitus in schizophrenics with active treatment with antipsychotics. That is supported by a study by **Wani*et al.*, (2015)** which found that, schizophrenia subjects (Not treated) did not show any significant elevation in plasma glucose when compared with the healthy control group.

The first reports of a link between antipsychotic medication and glucose dysregulations were made in the 1950s. In 1960s many studies showed that atypical antipsychotic drugs may be associated with a higher risk of impaired glucose tolerance (IGT) and diabetes as compared to conventional antipsychotics **(Scheen& De Hert, 2007).**

Lindenmayer*et al.*, (2003), conducted a study showed that olanzapine and clozapine-treated groups regularly revealed significant increases in glucose levels relative to haloperidol-treated patients. However, **Hedenmalm*et al.*, (2002),** found that clozapine, olanzapine and risperidone were significantly associated with glucose intolerance. In contrast, chlorpromazine and haloperidol were not associated with glucose intolerance.

Newcomer *et al*. (2002) have compared insulin sensitivity in patients on antipsychotics and in controls. They verified that increase in insulin resistance was strongly associated with increased adiposity. Additionally, a study by **Sowell *et al*., (2002)**, assessed insulin sensitivity in healthy individuals taking olanzapine and risperidone and they found that a higher resistance to insulin was correlated with increased body mass index (BMI). However, a significant number of cases occurs in non-obese patients, therefore, impairment of glucose metabolism cannot be completely explained by weight gain. According to FDA data, 25% of patients taking antipsychotics who developed DM did not present obesity or significant weight gain.

Significant increases in insulin resistance measures were detected for patients treated with olanzapine and clozapine, in comparison with patients taking typical antipsychotics only **(Figure 3).** No significant difference in insulin resistance were found for patients treated with risperidone or typical antipsychotics, as compared with control subjects **(Newcomer *et al.*, 2002)**

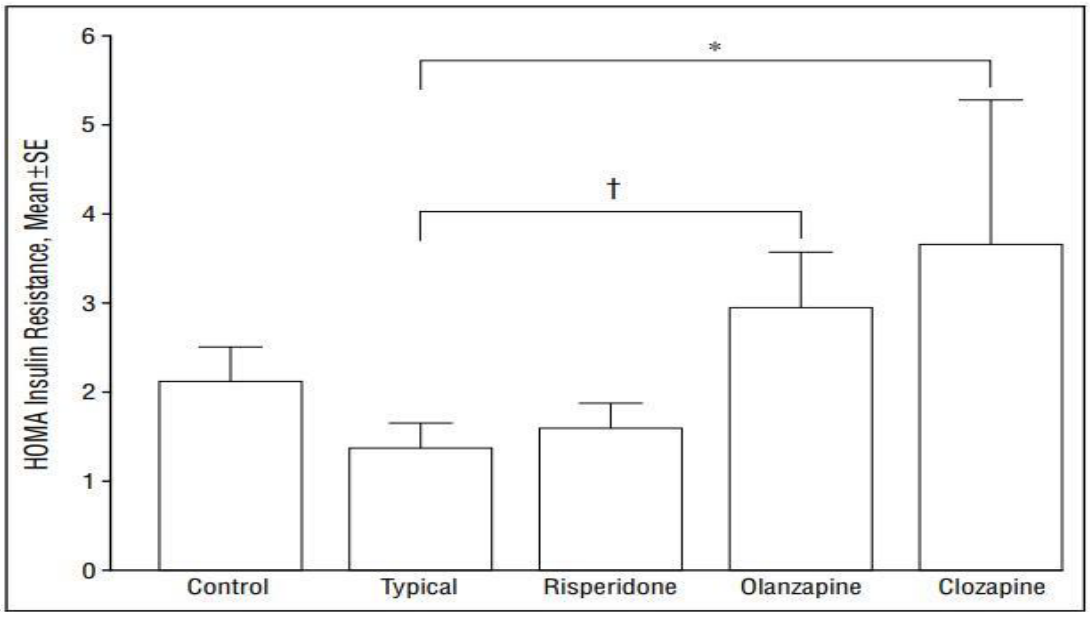

Figure 3: insulin resistance measures in schizophrenic patients treated with typical, risperidone, olnazepine and clozapine antipsychotics adapted from (Newcomer, *et al.*, 2002).

Furthermore, short term administration of the atypical antipsychotics (olanzapine and aripiprazole) induces insulin resistance in healthy subjects, but only olanzapine results in significant changes **(Kim *et al.*, 2010; Riordan *et al.*, 2011; Teff*et al.*, 2013).** The metabolic dysregulation caused by olanzapine significantly occurred in the absence of weight gain and psychiatric disease.

That suggests theses dysregulations are likely mediated by mechanisms separate from those regulating food intake as the healthy subjects did not show increases in food intake and hunger **(Teff*et al.*, 2013; Houseknecht*et al.*, 2007**; **Scheen,& De Hert, 2007).**

Wani, *et al*.(2015) found that non-diabetic schizophrenia patients treated with antipsychotic drugs e.g.(olanzapine, risperidone, haloperidol and aripiprazole) associated with adverse effect on glucose regulation, in the first 6 weeks the antipsychotics effects were comparable. While there was significant difference at 14 weeks was seen in olanzapine-treated group.

Scheen& De Hert, (2007), comparing the effects of six atypical antipsychotics on the development of a metabolic syndrome, dysglycemia (IFG/IGT) or diabetes among many schizophrenic patients. Aripiprazole was the only antipsychotic that was not associated to weight gain. Furthermore, it resulted in improved glucose tolerance and reduced incidence of metabolic syndrome in schizophrenic patients. In general, the rank order of risk observed for the second-generation antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of insulin resistance and hyperglycemia(**Table 3**).

Table 3: Glucose dysregulation in schizophrenic patients receiving atypical antipsychotic adapted from Scheen, & De Hert, (2007).

Drugs	Patient (n)	Weight change(kg)	Glucose alterations incidence (%)	New diabetes incidence (%)
Clozapine	23	+7.3	+31.1	8.7
Olanzapine	59	+6.9	+10.2	6.8
Quetiapine	31	+4.8	+16.1	6.5
Risperidone	58	+3.6	+6.9	1.7
Amisulpride	26	+4.7	-3.8	0
Aripiprazole	41	+4.8	-34.1	0

Olanzapine, clozapine and sertindole were associated with more substantial changes in the blood glucose levels. Additionally, olanzapine and sertindole treated patients were associated with a significantly greater change in glucose than ziprasidone, lurasidone which were followed in ranking by aripiprazole, risperidone, amisulpride, quetiapine, paliperidone and haloperidol (**Zhang *et al.*,2017).**

Type2 diabetes in patients treated with antipsychotics:

Antipsychotics have been shown to increase the risk of developing diabetes mellitus. The risk of type 2 diabetes mellitus is 1.3-fold higher in people with schizophrenia taking second-generation antipsychotic agents than in those taking first-generation drugs **(Smith *et al*., 2008).** Furthermore, several studies suggest that the risk of diabetes mellitus is different for different antipsychotics. For example, olanzapine and clozapine, and to a lesser extent quetiapine and risperidone, are associated with a significant increase in the risk of diabetes mellitus **(Smith *et al*., 2008; Riordan *et al.*, 2011)**.

Matching with the findings of **(Riordan *et al*.2011; Teff*et al*., 2013)** regarding olanzapine and clozapine effects on glucose metabolism, **Gianfrancesco*et al. (2002*)** suggests that olanzapine clozapine, and some conventional antipsychotics appear to increase the risk of acquiring or exacerbating type 2 diabetes and that the effect may vary by drug, which was significantly lower with aripiprazole, quetiapine, risperidone and ziprasidone treatment **(Yood*et al.*, 2009; Newcomer *et al*., 2002)**

However, database from the Food and Drug Administration (FDA), showed that the risk of diabetes mellitus was increased for olanzapine, risperidone, clozapine and quetiapine, whereas a decreased risk was found for haloperidol, aripiprazole and ziprasidone**(Berg *et al*., 2012).**

According to **(Nielsen *et al.*,2010),** diabetes are promoted in schizophrenia patients by initial and current treatment with olanzapine and mid-potency FGAs, as well as by current treatment with low-potency FGAs and clozapine, whereas current aripiprazole treatment reduced diabetes risk. Patients discontinuing olanzapine or mid-potency FGA had no increased risk of diabetes compared with patient not treated with the drugs at any time.

However, this could be explained by the fact that the weight that was gained initially is maintained throughout the course of the illness, adversely affecting insulin resistance.

Effects of antipsychotics on cardiovascular system:

Studies have shown increased risk of developing cardiovascular disease with the use of antipsychotics in schizophrenic patients. As showed and discussed in this paper that antipsychotics, in particular frequently cause weight gain, dyslipidemia and diabetes mellitus. Therefore, patients on antipsychotics are at high risk of metabolic syndrome, which is risk factors for cardiovascular disease. Antipsychotics differ in their effects on body weight, lipids and glucose regulation. However, the long-term effects of these antipsychotics on overall mortality and cardiovascular mortality when compared to the general population is two to three times higher **(Raedler 2010).**

A large epidemiological study done by **Dehert*et al.* (2012),** in which 74, 75 patients receiving antipsychotic monotherapy (44,218 users of first-generation drugs, 46,089 users of second-generation and 186,600 nonusers matched for cardiovascular disease risk based on patient data on file), showed a similar, dose-dependent increase in the risk of cardiovascular diseases and sudden cardiac death (SCD) for patients treated with either first-generation or second generation agents.

Systematic review done by **Silva *et al.*, (2017),** found that the use of antipsychotic agents was associated with an increased risk of cardiovascular adverse events (arrhythmia, acute myocardial associated with an increased infarction and mortality).

Atypical antipsychotics increase cardiovascular risk as a result of their tendency to cause weight gain and obesity, type 2 diabetes, dyslipidemia, prolongation of QT interval, and possibly myocarditis and pericarditis**(Krishnadev*et al.*, 2008).**

According to **Correll*et al.*, 2015,** SGA exposure was associated with a significantly increased all metabolic abnormalities, such as essential hypertension, diabetes mellitus, obesity, and hyperlipidemia, which were hardly associated with cardiovascular events, as there was a significantly increased risk for myocardial infarction (1.40), stroke (2.12), angina (1.32), hypertensive heart disease (1.56), coronary artery disease (1.52), and transient ischemic attack (1.70)(**Table 4**).

Table 4: metabolic and cardiovascular risk associated with SGA exposure at one year (Correll et al., 2015).

Outcome: diagnosis	Hazard ratio
Essential hypertension	1.27
Diabetes mellitus	1.73
Obesity	1.24
Stroke	2.12
Hypertensive heart disease	1.56
Myocardial infarction	1.40
Angina	1.32

Coronary artery disease	1.52
Transient ischemic attack	1.70
Hyperlipidemia	1.28

Daumit*et al.*, (2008), presented the change in 10 year risk of coronary heart diseases (CHD) of different antipsychotics treatments. Olanzapine was associated with a 0.5% increase and quetiapine, a 0.3% increase; whereas risk decreased in patients treated with risperidone, -0.6% and ziprasidone, -0.6%. These results indicate that the impact on 10-year CHD risk differs significantly between antipsychotic agents, with olanzapine producing the largest elevation in CHD risk of the agents studied.

Prolongation of the QT interval is associated with a greater risk of arrhythmia and sudden cardiac death. As many antipsychotics have long been linked to electrocardiographic abnormalities, beginning with case reports in the early 1960s. Subsequently, numerous studies have explored their effects on the QT interval **(Krishnadev*et al.*, 2008).**

At the U.S. Food and Drug Administration's (FDA) request. Pfizer (Drug Company) conducted a prospective, randomized study on 164 patients comparing the effect of ziprasidone, risperidone, olanzapine quetiapine, thioridazine and haloperidol on the QT interval (FDA, 2000). Thioridazine produced the greatest increase in QTc interval (36 ms), followed by ziprasidone (20ms), quetiapine (15ms), risperidone (12 ms), olanzapine (7 ms) and haloperidol (5 ms) (**Figure 4**).

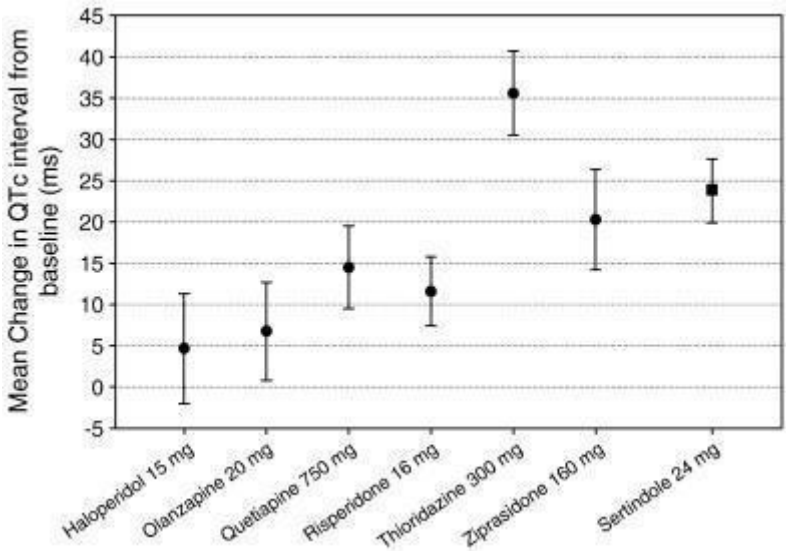

Figure 4: Mean change in QTc interval for patients treated with different antipsychotics adapted from (FDA 2000).

However, **Glassman, & Bigger Jr, (2001),** showed that the most marked risk is with thioridazine. Also, Pimozide, sertindole, and haloperidol have been documented to prolong the QT interval, cause torsade de pointes, and sudden death, While, there is no association with olanzapine, quetiapine, or risperidone. Ziprasidone does prolong the QT interval, but there is no evidence to suggest that this leads to torsade de pointes or sudden death

De Hert*et al.*, (2012), revealed that antipsychotic drugs associated with a high risk of QTc prolongation include the first-generation agents (pimozide, thioridazine and mesoridazine), and the second-generation drugs (sertindole, quetiapine and ziprasidone). Due to their heart adverse effects, mesoridazine and thioridazine have been removed from the market in the US and many other countries

The risk of sudden cardiac death increased with an increasing dose among current users of typical or atypical antipsychotic drugs. Among users of the typical agents, the incidence-rate ratios increased from 1.31 for persons taking low doses to 2.42 for those taking high doses. Among users of the atypical drugs, the incidence-rate ratios increased from 1.59 for persons taking low doses to 2.86 for those taking high doses. There was a dose–response trend for each of the six frequently prescribed drugs, a trend that was significant in the case of thioridazine and in the case of risperidone**(Ray *et al.*, 2009).**

Summary of Potential of Antipsychotic Medications to Cause Metabolic Syndrome

Table 7: summarizes the estimate potential of various antipsychotic medications to cause weight gain, the metabolic syndrome, and its individual components (Minus sign=cause changes, positive sign=doesn't cause changes)

Antipsychotics	Weight Gain	dyslipidemia	Insulin resistance	Metabolic syndrome	Type 2 diabetes	CVDs	
						CHD	QT elong
Clozapine	+++	++++	+++	High	+++	++	
Olanzapine	+++	+++	++++	High	++++		+
Thioridazine	++	+	-	Moderate			+++
Sertindole	++	+	+	Moderate			++
Chloropromazine	++	+++	-/-	Moderate			
Quetiapine	+	+	+	Moderate	-/+/+	+	+
Risperidone	+	+/-	+/-/-	Mild	-/+/+	-	+
Haloperidol	-/-	+	-/+	Low	-/-/		+
Amisulprid	+/-			Low			
Aripiprazole	+/-	-/-	+/-/+	Low	-/-/-		
Ziprasidone	-/-/-			Low	-/-	-	

Conclusion:

Patients with schizophrenia are at increased risk for developing the metabolic syndrome or its individual components due to their exposure to antipsychotic medications. Antipsychotics have been found to be strongly associated with weight gain, insulin resistance/glucose intolerance and dyslipidemia. Additionally, antipsychotic patients with metabolic syndrome are at high risk to develop type 2 diabetes and cardiovascular disease. Various antipsychotic medications have different liability to cause or exacerbate weight gain, and its individual components. Most of the reviewed articles showed that atypical antipsychotics are with higher risk to develop metabolic syndrome than typical antipsychotics. There is matching in research outcomes regarding the risk of metabolic syndrome components in antipsychotics patients. It has been found that clozapine and olanzapine cause the highest significant changes in weight gain, glucose intolerance, dyslipidemia and their complications. While Chlorpromazine causes significant changes in weight gain and lipid profile but no effect on insulin resistance. Moderate risk of metabolic syndrome showed with quetiapine, mild with risperidone, and low with aripiprazole, haloperidol and ziprasidone. Further, the risk of type 2 diabetes is higher in

patients taking atypical antipsychotics (specifically; olanzapine &clozapine) than in those taking typical drugs. Obviously that means, antipsychotic medications associated with greater weight gain are associated with greater risk of causing the MetS and their complications. Additionally, olanzapine produces the largest elevation in CHD risk which is largely correlated with its effect on weight gain and metabolic syndrome. However, drugs such as; thioridazine, haloperidol, quetapine, sertindole and ziprasidone are associated with a high risk of QT elongation which seems not correlated with weight gain suggesting different effect on heart could be synergistic with other side effect.

Recommendations:

Patients with schizophrenia commonly have problems in lifestyle such as, lack physical activity, and smoke cigarettes. Thus, many patients who are not taking drugs might already have one or more metabolic risk factors. Therefore, doctors should avoid prescribing an antipsychotic with a high metabolic liability even in individuals free of metabolic risk factors at baseline. Health provider and patient's family member should be informed about the risks and benefits of the antipsychotic drug treatment. FGAs with low metabolic liability should be considered in patients with metabolic problems not tolerating or not responding to SGAs with low metabolic liability before switching them to an SGA with high metabolic liability. Educate and encourage patients to maintain or adopt to a healthy lifestyle. Although screening for and monitoring of the metabolic side effects would be the responsibility ofthe physician prescribing the antipsychotic medication (usually a psychiatrist) and advice patient's to follow a dietitian and weight loss program.

المستخلص: تعد متلازمة التمثيل الغذائي من أهم تحديات الصحة العامة في جميع أنحاء العالم. يتم تعريف بواسطة منظمات صحية مختلفة كحالة مرضية تتميز بالسمنة في البطن ومقاومة الأنسولين وارتفاع ضغط الدم وفرط شحميات الدم. الشحوم المركزية هي سمة أساسية لمتلازمة التمثيل الغذائي ، كما يتضح من العلاقة القوية بين انتشار متلازمة التمثيل الغذائي ومحيط الخصر. يهدف هذا المشروع إلى مراجعة مكونات متلازمة التمثيل الغذائي ومراجعة البحوث التي تصف إمكانات الأدوية المضادة للذهان للتسبب في زيادة الوزن وخلل الدهون في الدم وخلل الجلوكوز وهي مكونات متلازمة التمثيل الغذائي. المرضى الذين يعانون من مرض انفصام الشخصية معرضون بشكل متزايد لخطر الإصابة بمتلازمة التمثيل الغذائي أو مكوناته الفردية بسبب تعرضهم للأدوية المضادة للذهان. بالإضافة إلى ذلك ، فإن المريض المصاب بمرض الذهان و بمتلازمة التمثيل الغذائي معرض لخطر كبير للإصابة بمرض السكري من النوع 2 وأمراض القلب والأوعية الدموية.أظهرت معظم المقالات التي تمت مراجعتها أن مضادات الذهان غير التقليدية تكون أكثر عرضة لخطر الإصابة بمتلازمة التمثيل الغذائي مقارنة بمضادات الذهان التقليدية. لقد وجد أن كلوزابينوأولانزابين يتسببان في حدوث تغييرات كبيرة في زيادة الوزن ، وخلل الجلوكوز ، وخلل الدهون في الدم ومضاعفاتهم. علاوة على ذلك ، فإن خطر الإصابة بالنوع الثاني من داء السكري يكون أكبر في تناول المريض لمضادات الذهان غير التقليدية (على وجه التحديد ؛ أولانزابينوكلوزابين) مقارنة بأولئك الذين يتناولون أدوية التقليدية.

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