

# Potential Toxic Effects of Olanzapine on Metabolic Parameters in *de Novo* Paranoid Schizophrenic Patients. The Role of Adjunctive Aripiprazole: Clinical and Experimental Study

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**How to cite this paper:** Al-Sayed, H.M. and Soliman, W.I. (2019) Potential Toxic Effects of Olanzapine on Metabolic Parameters in *de Novo* Paranoid Schizophrenic Patients. The Role of Adjunctive Aripiprazole: Clinical and Experimental Study. *Occupational Diseases and Environmental Medicine*, 7, 91-113.

<https://doi.org/10.4236/odem.2019.73008>

**Received:** June 3, 2019

**Accepted:** August 18, 2019

**Published:** August 21, 2019

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## Abstract

**Background:** Approximately 75% of all deaths in people with schizophrenia are caused by physical illness with cardiovascular disease [CVD] being the commonest cause of death. Factors predisposing people with schizophrenia to CVD include antipsychotic medication. **Aim of Work:** The aim of this study was to detect metabolic syndrome and its components in *de novo* paranoid schizophrenics on olanzapine therapy and the metabolic benefits of addition of aripiprazole, clinically and experimentally. **Methodology:** 1) Clinical study: 200 Outpatients suffered from *de novo* paranoid schizophrenia according to 10<sup>th</sup> International Classification of Psychiatric Disorders, Research Criteria [ICD10 RC] were included in the study. None of them had any component of metabolic syndrome. They were maintained on olanzapine [10 - 20 mg]. Patients were assessed clinically, psychometrically using Scale for the Assessment of Negative [SANS] and Positive [SAPS] Symptoms and metabolically at base line and after 6 months. Patients who had metabolic syndrome after 6 month of starting olanzapine therapy, were randomly divided into two groups according to added regime to maintained olanzapine: Group 1: olanzapine [10 mg/day] + placebo [empty hard gelatin capsule]. Group II: olanzapine [10 mg/day] + aripiprazole [10 mg/day]. 2) Experimental study: 40 male albino rats were randomly equally divided into 4 groups: Group 1 [control group]: received a standard diet, Group II [olanzapine treated]: received olanzapine at a dose of 0.5 mg/kg/day, Group III [aripiprazole treated]: received aripiprazole at a dose of 2 mg/kg/day, Group IV [combined olanzapine and aripiprazole treated]: received olanzapine at a dose of 0.5 mg/kg/day combined with aripiprazole at a dose of 2 mg/kg/day orally. The duration of

the study was 16 weeks. All treated rat groups were assessed for metabolic parameters, liver enzymes and histopathology. **Results:** Clinically, after the 6 months of olanzapine treatment [mean dose 12.75 mg], there was significant increase [ $p < 0.001$ ] in weight, body mass index, triglyceride, total cholesterol, and fasting blood glucose level compared to base line level of these parameters (**Table 1**). 32 patients [16%] suffered from metabolic syndrome after 6 months of olanzapine therapy. After 3 months of aripiprazole, [10 mg/day], addition to maintained olanzapine therapy to patients suffered from metabolic syndrome, there was significant [ $p < 0.001$ ] improvement in tested parameters (**Table 2**). Experimentally, the rats in group II [olanzapine treated rats] had significantly higher body weight [ $p = 0.002$ ], liver weight [ $p < 0.001$ ], metabolic parameters [ $p < 0.001$ ] and liver enzymes [ $p < 0.001$ ] than controls. Group 1v [combined olanzapine and aripiprazole treated rats] had significant decrease in metabolic parameters and liver enzymes in comparison to olanzapine treated rats (**Table 3**). Histopathologically, liver fat cells were significantly [ $p < 0.001$ ] present in the olanzapine-only [8 rats] treatment group compared to group 1v [3 rats] and group 11 [zero]. Liver fat cells were higher in number and larger in size in group 1 compared to group 1v and group 1. **Conclusion and Recommendation:** Olanzapine treatment was found to be associated with risk factors of metabolic syndrome clinically and experimentally and its hepatic manifestation of non-alcoholic fatty liver disease in wister rats. Improvements were observed clinically and experimentally in metabolic measures, liver enzymes and liver histopathology by addition of aripiprazole. Patients on olanzapine therapy must be followed regularly regarding metabolic parameters, hepatic, cardiac and cerebrovascular morbidity, with urgent interference with early manifestations. It is recommended to check liver enzymes regularly for those patients kept on atypical antipsychotic drug [olanzapine].

### Keywords

Olanzapine, Aripiprazole, Paranoid Schizophrenia, Metabolic Syndrome, Fatty Liver Disease

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## 1. Introduction

Schizophrenia is a psychotic illness that affects approximately 1% of the population. Mortality rates are increased two- to four-fold in people with schizophrenia and life expectancy is reduced by 10 - 20 years [1] [2] [3]. Approximately 75% of all deaths in people with schizophrenia are caused by physical illness with cardiovascular disease being the commonest cause of death [1].

Since their introduction in 1990, atypical antipsychotics [AAPs] have become the most common treatment for patients with a variety of psychotic disorders [4]. Atypical antipsychotics used for the treatment of schizophrenia offer significant advantages over conventional compounds, particularly because they are

**Table 1.** Some metabolic parameters in studied patients at baseline and after six month of olanzapine therapy using Paired t test.

	Baseline [200] Mean $\pm$ SD	After 6 m [200] Mean $\pm$ SD	Paired t test	P value
Wt [kg]	64.84 $\pm$ 15.8	71.09 $\pm$ 12.96	10.51	<0.001**
wc [cm]	82.54 $\pm$ 8.84	86.35 $\pm$ 8.28	5.48	<0.001**
BMI	24.46 $\pm$ 10.59	24.71 $\pm$ 10.52	3.23	<0.001**
FBG	84.28 $\pm$ 7.95	90.73 $\pm$ 13.09	6.08	<0.001**
TG level	136.54 $\pm$ 35.09	152.54 $\pm$ 38.16	4.43	<0.001**
Total blood Cholesterol	175.31 $\pm$ 21.48	187.48 $\pm$ 29.74	4.67	<0.001**
HDLC	46.19 $\pm$ 24.41	41.07 $\pm$ 25.42	20.85	<0.001**
HbA1c	5.63 $\pm$ 3.29	5.71 $\pm$ 3.35	7.36	<0.001**
SBP	112.43 $\pm$ 25.07	119.91 $\pm$ 23.84	7.27	<0.001**
DBP	77.11 $\pm$ 17.83	81.5 $\pm$ 17.14	13.51	<0.001**

SD: Standard deviation; t test: student t test; \*\*: Highly significant [P < 0.001].

**Table 2.** Placebo versus aripiprazole in metabolic syndrome patients maintained on olanzapine for three months.

	Olanzapine + placebo (number = 16)	Olanzapine+ aripiprazole (number = 16)	St t test	P
Weight [kg]				
0 m	78.86 $\pm$ 3.44	77.47 $\pm$ 2.79	1.26	0.22
3 m	81.37 $\pm$ 1.71	74.24 $\pm$ 1.38	13.0	<0.001**
Paired t test	2.90	3.80		
P	0.011*	0.002**		
Waist circumference [cm]				
0 m	91.91 $\pm$ 3.15	90.24 $\pm$ 3.75	1.36	0.19
3 m	92.23 $\pm$ 2.39	89.79 $\pm$ 1.10	3.71	0.001**
Paired t test	0.43	0.52		
P	0.67	0.61		
BMI				
0 m	24.83 $\pm$ 2.36	24.88 $\pm$ 2.12	0.07	0.94
3 m	24.92 $\pm$ 2.35	24.74 $\pm$ 2.13	0.22	0.83
Paired t test	0.36	0.93		
P	0.72	0.37		

## Continued

Fasting blood glucose				
0 m	112.08 ± 2.05	111.89 ± 2.10	0.25	0.81
3 m	112.04 ± 2.02	104.73 ± 7.93	3.58	0.001**
Paired t test	2.42	3.17		
P	0.029*	0.006**		
Serum Triglyceride				
0 m	168.94 ± 4.33	167.56 ± 3.41	1.0	0.33
3 m	182.31 ± 11.59	145.25 ± 8.08	10.49	<0.001**
Paired t test	4.91	11.03		
P	<0.001**	<0.001**		
Total blood Cholesterol				
0 m	185.0 ± 5.93	186.17 ± 6.60	0.53	0.60
3 m	190.06 ± 8.19	180.13 ± 5.63	4.0	<0.001**
Paired t test	3.15	3.31		
P	0.007**	0.005**		
HDLC				
0 m	37.94 ± 2.84	38.09 ± 6.32	0.087	0.93
3 m	37.13 ± 2.45	38.34 ± 6.15	0.73	0.47
Paired t test	1.98	1.29		
P	0.066	0.22		
Hb <sub>A1c</sub>				
0 m	5.85 ± 0.63	5.79 ± 0.62	0.26	0.80
3 m	5.92 ± 0.66	5.81 ± 0.58	0.52	0.61
Paired t test	1.74	0.31		
P	0.10	0.76		
SBP				
0 m	123.88 ± 3.91	123.54 ± 3.74	0.25	0.81
3 m	126.02 ± 3.24	122.8 ± 3.44	2.73	0.011*
Paired t test	1.70	2.16		
P	0.11	0.047*		
DBP				
0 m	82.23 ± 1.83	81.78 ± 2.04	0.67	0.51
3 m	84.36 ± 3.48	80.76 ± 2.40	3.4	0.002**
Paired t test	2.09	1.35		
P	0.054	0.20		

SD: Standard deviation \*\*: Highly significant [P < 0.001]; t test: student t test \*: significant [P < 0.05].

**Table 3.** Metabolic parameters and liver function tests in rats of different studied groups using ANOVA test.

	Control group [10] Mean ± SD	Group 2 [10] olanzapine Mean ± SD	Group 3 [10] aripiprazole Mean ± SD	Group 4 [10] Olanzapine +aripiprazole Mean ± SD	F test	P value
Baseline wt[gm]	179.5 ± 14.81	182.5 ± 20.17	181.2 ± 13.29	177.9 ± 17.79	0.15	0.93
Wt at End of study [gm]	247.2 ± 28.92	288.1 ± 51.05\$	221.4 ± 20.9^	253.3 ± 36.62^	5.78	0.002**
Liver wt[gm]	12.095 ± 0.23	13.76 ± 0.45\$	12.22 ± 0.15^	13.01 ± 0.38\$^€	55.87	<0.001**
total Cholesterol	54.8 ± 20.71	77.68 ± 21.5\$	50.91 ± 22.15^	62.8 ± 4.59	4.0	0.015*
FBS	124.97 ± 5.25	141.4 ± 10.11\$	126.0 ± 7.67^	129.7 ± 8.58^	8.66	<0.001**
Triglycerides	130.0 ± 8.19	215.4 ± 13.43\$	133.1 ± 11.17^	171.2 ± 16.92\$^€	97.08	<0.001**
ALT	24.32 ± 1.26	67.3 ± 1.63\$	27.46 ± 1.72\$^	58.23 ± 1.1\$^€	2230.0	<0.001**
AST	51.59 ± 1.42	89.64 ± 1.73\$	54.64 ± 1.43\$^	73.41 ± 1.57\$^€	1319.8	<0.001**
AIP	71.73 ± 1.24	79.07 ± 1.37\$	74.22 ± 0.90\$^	76.55 ± 1.47\$^€	61.88	<0.001**
Bilirubin	0.49 ± 0.03	0.81 ± 0.08\$	0.57 ± 0.14^	0.64 ± 0.13\$^	16.88	<0.001**

\$: significant & control group SD: Standard deviation; ^: significant & group 2 t test: student t test; €: significant & group 3 \*\*: Highly significant [P < 0.001]; \*: significant [P < 0.05].

associated with fewer extrapyramidal symptoms than conventional antipsychotics [5]. However, compelling evidence indicates that the use of AAPs is related to potentially serious adverse metabolic effects, including obesity, dyslipidemia, hyperglycemia, and type 2 diabetes mellitus [6] [7]. These metabolic disturbances may lead to an increase in the risk of cardiovascular diseases [CVD] and premature mortality [8].

Olanzapine is an atypical antipsychotic of the thienobenzodiazepine class. Although structurally and functionally related to clozapine, it possesses a more favourable side-effect profile [9] [10]. Recently, the scientists have tried to elucidate the mechanism of toxicities associated with olanzapine [11].

Aripiprazole (ARI, 7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2[1H]-one) is a commonly prescribed atypical antipsychotic drug used to treat psychosis such as schizophrenia, episodes associated with bipolar disorder, delayed sleep phase syndrome, and irritability in children with autism [12] [13].

Metabolic syndrome [MetS] is defined by a combination of central obesity, high blood pressure, low high-density lipoprotein [HDL] cholesterol, elevated triglycerides and hyperglycaemia. In the general population, these clustered risk factors have been associated with the development of CVD and excess mortality [14] [15] [16].

Current definitions [17] [18] for MetS are aimed at being easy to use in clinical settings and share similar diagnostic thresholds [19]. As a prevalent condition and predictor of CVD across racial, gender and age groups, MetS provides the opportunity to identify high-risk populations and prevent the progression of some major causes of morbidity and mortality [19].

Non-Alcoholic fatty liver disease [NAFLD], is considered the hepatic manifestation of metabolic syndrome [MetS] [20]. NAFLD is common and has a spectrum of liver changes beginning with simple fatty liver and progressing to steatohepatitis, cirrhosis and liver failure. Alcoholic fatty liver disease [AFLD] is frequently present along with the components of metabolic syndrome and, hence, is generally regarded as a manifestation of metabolic syndrome [21]. Non-alcoholic steatohepatitis [NASH] is recognized as a progressive form of fatty liver disease, has been documented to have the potential to progress to cirrhosis and hepatocellular carcinoma [21] [22].

The aim of this study was to detect MetS and its components in people with *de novo* paranoid schizophrenia on olanzapine therapy. We aimed to assess the safety and the metabolic benefits of addition of aripiprazole to olanzapine treated patients suffered from metabolic syndrome. Experimentally, we aimed to investigate the metabolic effect of olanzapine and its hepatic effects in wister rats and the effect of adjunctive aripiprazole.

## 2. Subject and Method

### Drugs

- Olanzapine 5, 10 mg tablet [Zyprexa] obtained from Eli Lilly pharmaceutical company.
- Aripiprazole 10 mg tablet [Aripiprex] obtained from Al Andalous pharmaceutical company.

### 2.1. Clinical Study

Subjects were recruited from neuro-psychiatric outpatient of Benha University hospital and Benha psychiatric hospital from 1<sup>st</sup> of January to 30<sup>th</sup> of December 2018. The study was approved by the ethical committee of Benha University.

200 Outpatients suffered from *de novo* paranoid schizophrenia according to ICD10 RC [23] were included in the study after providing written informed consent.

#### Exclusion criteria:

- Patients with any component of metabolic syndrome. They were diagnosed according to the recommendation of the International Diabetes Federation [IDF] Task Force on Epidemiology and Prevention [joint interim statement in 2009] [19],
- Substance abuse,
- Pregnant and lactating mothers,
- Any co-morbid medical, neurological and psychiatric illness

At base line [0 month], and 6 months, all of the following parameters were performed:

- Diagnostic evaluation by two different psychiatric consultants.
- Symptom rating scales using Scale for the Assessment of Negative [SANS] [24] and Positive [SAPS] Symptoms [25].

- Medical history and examination.
- Weight [Wt] [kg], height [cm], body mass index [BMI], and waist circumference [suprailiac] [wc] [cm].
- Laboratory examination for fasting blood glucose [FBG], glycosylated hemoglobin [HbA1c], total blood cholesterol, triglyceride level [TG], and high density lipo-protein cholesterol [HDL C].

Fasting serum glucose [mg/dl] was determined colorimetrically using a test reagent kit [Biolabo SA, France] according to manufacturer's method.

Glycosylated hemoglobin was estimated by a commercial kit [BioSystem SA, Barcelona, Spain] according to manufacturer's method.

Total blood cholesterol, serum triglyceride [TG] and HDL were estimated using test reagent kits [Spinreact, Spain] and expressed as mg/dl according to manufacturer's method.

All subjects were maintained on olanzapine [10 - 20 mg]. Patients had to be maintained on stable dose of olanzapine for at least 3 months. All patients had psycho-education program and their care givers concerning appropriate diet and physical activity for the patients.

Patients who had metabolic syndrome after 6 months of starting olanzapine therapy were randomly divided into two groups according to added regime to maintained olanzapine:

Group I: Olanzapine [10 mg/day] + placebo [prepared starch tablet similar in shape to aripiprazole tablet]

Group II: Olanzapine [10 mg/day] + aripiprazole [10 mg/day]

After three months, the two groups were subjected to assessment of all previous parameters.

## 2.2. Experimental Study

### 2.2.1. Ethical Consideration of Study

The experimental procedures and the use of laboratory animal were approved by the Animal Research Committee in Zagazig University. Painless procedures were conducted. Animal housing and handling were ethically considered.

### 2.2.2. Animals

The current study was performed using 40 albino rats [male, 150 - 180 g, 12 - 16 weeks-old] obtained from the Faculty of Veterinary Medicine, Zagazig University. Rats were housed in stainless steel cages and maintained under standardized environmental conditions [25°C] away from any stress with a 12-hr light/dark cycle and 50% humidity.

All rats had *ad libitum* access to standard rodent chow and filtered water. Rats were acclimatized for 1 week before use in the experiments.

Animals were randomly equally divided into 4 groups:

Group I [control group]: received a standard diet, for 16 weeks

Group II [olanzapine treated]: received olanzapine at a dose of 0.5 mg/kg/day, according to the drug calculation formula [26] [27] [28]. Each tablet [5 mg], was

dissolved in 10 ml normal saline, and each rat received 1 ml/kg/day of the dissolved drug via gastric tube to ensure that no drug loss occurs [29] [30].

Group III [aripiprazole treated]: received aripiprazole at a dose of 2 mg/kg/day, according to the drug calculation formula [26] [27] [28]. Each tablet [10 mg], was dissolved in 10 ml normal saline, and each rat received 2 ml/kg/day of the dissolved drug via gastric tube [31].

Group IV [combined olanzapine and aripiprazole treated]: received olanzapine at a dose of 0.5 mg/kg/day combined with aripiprazole at a dose of 2 mg/kg/day by gastric tube daily for 16 weeks.

The duration of the study was 16 weeks. Male rats were selected to obviate potential interactions with ovarian hormones previously found to influence primary outcome measures [32] [33].

Body weight was recorded once weekly. By the end of the treatment period, animals were then fasted for 12 h and blood samples were withdrawn from the retro-orbital plexus for the Assessment of metabolic and biochemical parameters. Then all animals were scarified under light ether anaesthesia. The liver of each rat was removed and weighed then stained for histopathological studies.

### 2.2.3. Assessment of Metabolic and Biochemical Parameters

- Fasting serum glucose [mg/dl] was determined colorimetrically using a test reagent kit [Biolabo SA, France]
- Total blood cholesterol and serum triglyceride [TG] were estimated using test reagent kits [Spinreact, Spain] and expressed as mg/dl
- Determination of serum bilirubin and some liver enzymes: Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], and alkaline phosphatase [ALP] using a kit supplied by Human, Germany, according to the instructions of the supplier.

### 2.2.4. Histopathological Examinations

- Liver slides for histopathological study were prepared and stained with routine hematoxylin and eosin staining [34].

## 2.3. Statistical Analysis

Data were expressed as mean  $\pm$  standard error of mean. Comparison between the mean values of different groups was carried out using one-way analysis of variance, Data were analyzed by Statistical Package of Social Science [SPSS], software version 22.0 [35].

The  $P < 0.05$  was considered to indicate statistical significance between groups.

## 3. Results

### 3.1. Clinical Results

After 6 months of olanzapine treatment [mean dose 12.75 mg], there was significant increase in weight [Wt], waist circumference [wc], body mass index [BMI],



triglyceride [TG], total cholesterol, fasting blood glucose level [FBG], glycosylated hemoglobin [HbA1C], systolic blood pressure [SBP] and diastolic blood pressure [DBP] compared to base line level of these parameters. There was a significant decrease in high-density lipoprotein cholesterol [HDL-C] compared to base line level.

32 patients [16%] suffered from metabolic syndrome after 6 months of olanzapine therapy.

After 3 months of aripiprazole, [10 mg/day], addition to maintained olanzapine therapy to patients suffered from metabolic syndrome, there was significant decrease in body weight, waist circumference, triglyceride, total cholesterol, and fasting blood glucose level compared to placebo control group [maintained on olanzapine therapy].

Aripiprazole treatment did not significantly changed [SANS] [ $12.6 \pm 1.01$ ] and [SAPS] [ $10.03 \pm 1.34$ ] score. Akathisia in some cases managed by short period of small dose of benzodiazepine.

## 3.2. Experimental Results

### Body Weight and Liver Weight

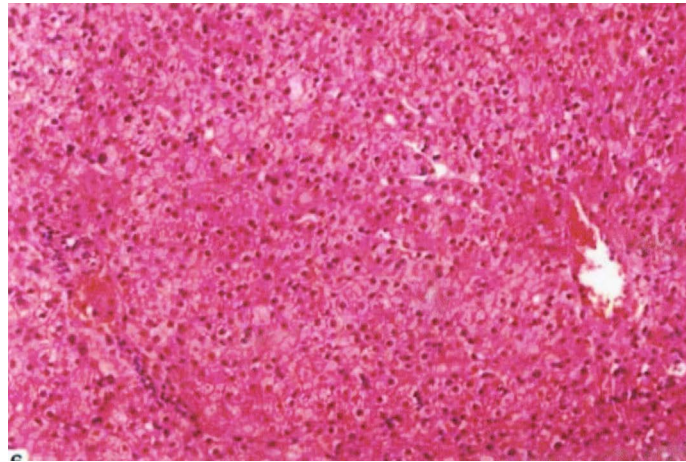
After 16 weeks, The rats in group II [olanzapine treated rats] had significantly higher body weight and liver weight than controls [group I], group III [aripiprazole treated rats] and group IV [combined olanzapine and aripiprazole treated rats] **Table 3**. In contrast, the rats in group IV [combined olanzapine and aripiprazole treated rats] had significantly lower body weight and liver weight than those with olanzapine-treated group [group II].

The present study revealed increased level of metabolic parameters [total cholesterol, fasting blood glucose level, triglyceride] and liver enzymes [Alanine aminotransferase [ALT], Aspartate aminotransferase [AST] and alkaline phosphatase [ALP]] in group II [olanzapine treated rats] when compared with other groups.

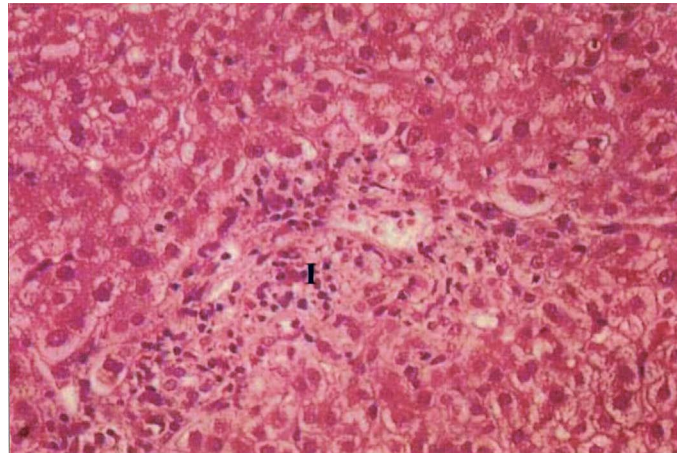
Histological examination of liver in control group showed the maintenance of normal lobular architecture, normal histology (**Figure 1**). Histopathological finding in olanzapine treated rat group (**Figure 3**) in the present study showed a picture of non-alcoholic liver disease in the form of ballooning degeneration, inflammatory infiltrates and accumulated lipid vacuoles in hepatocytes [steatosis]. Many Kupffer cells were also present. It had larger total fat cell areas than the control. There was no significant portal inflammation or hepatocytes damage at aripiprazole treated rats (**Figure 2**). Combined olanzapine- and aripiprazole-treated rats (**Figure 4**) showed less prominent and less severe picture of non-alcoholic liver disease compared to olanzapine treated rats [the portal tract showed small aggregates of chronic inflammatory cells, fewer Kupffer cells, few fatty changes and ballooning degeneration].

## 4. Discussion

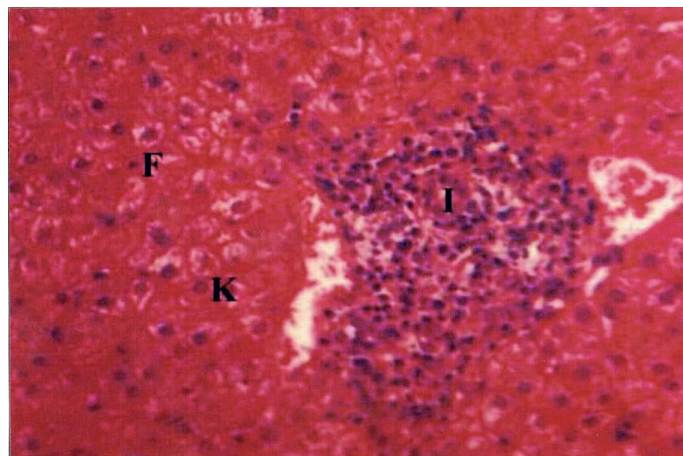
People with severe mental illness [SMI], including schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder [MDD],



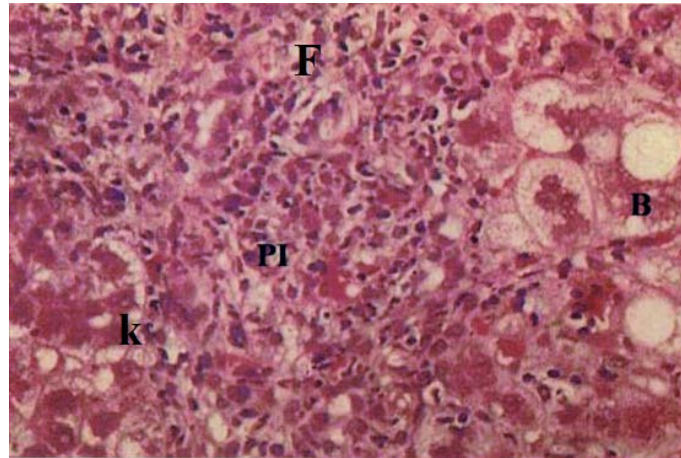
**Figure 1.** A photomicrograph of hepatic tissue of adult albino rat of control group [received a standard diet, for 16 weeks], showing normal hepatic tissue [H × & E × 200].



**Figure 2.** A photomicrograph of hepatic tissue of adult albino rat of aripiprazole group [at a dose of 2 mg/kg/day for 16 weeks], showing few inflammatory cells [I] in the portal tract [H × & E × 300].



**Figure 3.** A photomicrograph of hepatic tissue of adult albino rat of olanzapine group [at a dose of 0.5mg/kg/day for 16 weeks] showing portal tract infiltration with inflammatory cells [I], hyperplasia of kupffer cell [K] with focal fatty changes [F] [H × & E × 200].



**Figure 4.** A photomicrograph of liver tissue of adult albino rat of combined aripiprazole [at a dose of 2 mg/kg/day for 16 weeks], and olanzapine [at a dose of 0.5 mg/kg/day for 16 weeks] showing few inflammatory cells [PI] in the portal tract, fewer Kupffer cells [K], few fatty changes [F] and ballooning degeneration [B] [H × & E × 300].

experience a two-three times higher mortality rate than the general population [36] [37]. This mortality gap translates into a 10 - 20-year shortened life expectancy [38] [39] and appears to be widening [40]. About 60% of the excess mortality observed in SMI is due to physical comorbidities, predominantly cardiovascular diseases [CVD] [41]. Factors predisposing people with SMI to CVD include antipsychotic medication and unhealthy lifestyles [42] as well as their reduced likelihood to receive standard levels of medical care [43] [44] [45].

200 Outpatients suffered from *de novo* paranoid schizophrenia according to ICD10 RC [23] were included in the study. Few studies have included people with a first episode of psychosis and yet weight gain occurs commonly and rapidly in this group of individuals after treatment initiation. We have also specifically included people with first-episode psychosis, where the aim of the intervention may be the prevention of weight gain rather than weight loss [46].

No Patient had any component of metabolic syndrome. The diagnosis of metabolic syndrome [MetS] was determined based on the recommendation of the International Diabetes Federation Task Force on Epidemiology and Prevention [joint interim statement in 2009] [19]. According to the established definition, metabolic syndrome was identified in persons who met at least 3 out of 5 criteria

- 1) Waist circumference  $\geq 94$  cm in males;  $\geq 80$  cm in females-3
- 2) Fasting glucose  $\geq 100$  mg/dl [5.5 mmol/l] or diabetes-2 treatment
- 3) Triglycerides  $\geq 150$  mg/dL [1.7 mmol/l] or drug treatment-3 for elevated triglycerides
- 4) HDL cholesterol  $\leq 40$  mg/dL [1.7 mmol/l] in males,  $\leq 50$  mg/dl [1.3 mmol/l] in females.
- 5) Systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg, or drug treatment for hypertension.

36 [15.3%] paranoid schizophrenic patients were excluded. 15 of them suffered from metabolic syndrome and 10 had one component and 11 had two

components of metabolic syndrome according to the International Diabetes Federation Task Force on Epidemiology and Prevention [joint interim statement in 2009] [19]. Comparing MetS in first versus multi-episode patients within illness subgroups, first episode psychosis patients [13.7%] had a significantly lower MetS risk than those with multi-episode schizophrenia [34.2%]. Although mean age predicted MetS prevalence. First episode was also a unique predictor of lower MetS [47].

Several studies indicated that obesity is two to three times more prevalent among people with schizophrenia than in the general population and this occurs early in its natural history [48].

After the 6 months of olanzapine treatment [mean dose 12.75 mg], there was significant increase in weight, body mass index, triglyceride, total cholesterol, and fasting blood glucose level compared to base line level of these parameters (Table 1).

Olanzapine treated patients [200 patients] for 6 months demonstrated a main weight gain of 6.25 kg in this study. Osser *et al.* [49] found 12 lb [pound] as a main weight gain after 12 weeks of a main olanzapine dose [13.8 mg]. Another study found that, 94% of day-treatment patients treated with olanzapine [main dose 14.1 mg] experienced weight gain of greater than 7% and the main weight gain was 22.1 lb over 7 months [50].

This is in line with many systematic reviews and meta-analyses which reported that olanzapine and clozapine induce most severe weight gain when compared with other antipsychotics [51] [52] [53] [54].

Experimentally, Olanzapine treated rats had significantly more body weight and liver weight compared to other three studied groups, which was corresponding with previous reports [54] [55] [56] [57] [58].

Weight gain is a common adverse effect of antipsychotic medication, affecting between 15% and 72% of patients [59] Most weight gain occurs early in treatment. Between 37% and 86% of those experiencing a first episode of psychosis also experiencing more than 7% weight gain in 12 months [60], often occurring within 12 weeks of treatment initiation [61].

In a trial to explain the mechanism of olanzapine-induced weight gain, several animal studies have found that olanzapine could modulate histaminergic neurotransmission for the regulation of food intake and weight gain in rats [62] [63]. Further evidence showed that weight gain and obesity associated with olanzapine are mediated by activation of the hypothalamic AMP-activated protein kinase [AMPK] pathway via blockade of H<sub>1</sub> receptors [64] [65], and [66]. In fact, a recent study revealed an association between polymorphisms in the AMPK gene and weight gain induced by olanzapine and clozapine [67]. Additionally, it was reported that olanzapine down-regulates the anorexigenic neuropeptide proopiomelanocortin [POMC], but up-regulates the orexigenic neuropeptide Y [NPY], in the arcuate nuclei of the hypothalamus [Arc] [68] [69]

There was significant increase in serum triglyceride level in olanzapine treated patients for 6 months. The main increase was 16 mg/dl. Olanzapine treated rats



in our study showed significant more triglyceride level than other studied groups. Hypertriglyceridemia has been linked to olanzapine therapy [70] [71]. Atmaca *et al.* [72] observed a significant increase in weight and triglyceride levels in olanzapine-treated groups. Sheitman *et al.* [73] reported an increase in serum triglyceride from baseline to 16-month re-assessment where triglycerides increased more than 40%.

There is evidence that AAPs may cause hypertriglyceridemia through several possible mechanisms: 1) a direct effect on triglyceride metabolism either by stimulation of hepatic triglyceride production and secretion or by inhibition of lipoprotein lipase-mediated triglyceride hydrolysis and 2) an indirect mechanism associated with obesity and insulin resistance [74].

Olanzapine treated patients for 6 months demonstrated a main increase in fasting blood glucose [6.35 mg], cholesterol level [12.17 mg] and decrease in HDLC [5.12 mg]. Olanzapine treated rats in our study showed significant more fasting blood glucose, cholesterol level than other studied groups. Abnormalities of triglyceride and HDL metabolism are an early manifestation of insulin resistance, often detectable even before the development of abnormal postprandial or fasting glucose levels [75].

It has been found that the metabolic disturbances associated with the use of atypical antipsychotics are a direct consequence of alteration of insulin sensitivity. Impaired parasympathetic regulation of  $\beta$ -cell activity mediated by blockade of histaminergic and muscarinic receptors may contribute to an increased metabolic risk [76].

32 patients [16%] suffered from metabolic syndrome after 6 months of olanzapine therapy according to the recommendation of the International Diabetes Federation [IDF, 2009] Task Force on Epidemiology and Prevention [19]. MetS risk was significantly higher with clozapine, followed by olanzapine. [44] [77].

Olanzapine, can induce metabolic disturbances, such as obesity, hypertriglyceridemia, glucose dysregulation, and in some studies, elevated serum cholesterol levels [78] [79]. These metabolic disturbances may lead to an increase in the risk of cardiovascular diseases and premature mortality [8]. Despite these problems, the use of metabolically potent antipsychotic drugs is widespread, arguably due to superior therapeutic efficacy compared with antipsychotics with more favorable metabolic profiles [80].

While switching to a more weight-neutral atypical antipsychotic agent offers promise in halting or reversing weight gain, many patients and their clinicians are reluctant to risk a worsening or return of psychotic symptoms and risk relapse [81].

Experimentally, there was no significant difference between aripiprazole [ARI] treated group and control group as regards to metabolic changes in rats.

This is in accordance with Greenaway and Elbe.'s review study [82], in which they discussed 4 prospective randomized controlled trials and 9 open-label prospective studies about aripiprazole. They found that in all 4 randomized controlled trials, there was no significant increase in body weight.

ARI is associated with a lower risk of metabolic and cardiac issues such as weight gain, diabetes, and dyslipidemia than most SGAs [83]. Also, Sayyaparaju *et al.* [84] stated that aripiprazole was associated with minimal weight gain and metabolic changes [dyslipidemia, elevated serum triglycerides and impairments in glycemic control] unlike most second-generation antipsychotics.

The lowest MetS prevalence for aripiprazole is noteworthy, as antipsychotics with lower cardiometabolic risk profiles in short-term studies are often prescribed for higher risk patients in clinical care, which may lead to a not reduced or even increased cardiometabolic risk in naturalistic settings [85].

After 3 months of aripiprazole, [10 mg/day], addition to maintained olanzapine therapy to patients suffered from metabolic syndrome, there was significant decrease in body weight, triglyceride, total cholesterol, and fasting blood glucose level compared to placebo-controlled group [maintained on olanzapine therapy]. Aripiprazole treatment did not significantly change [SANS] [ $12.6 \pm 1.01$ ] and [SAPS] [ $10.03 \pm 1.34$ ] score. Combined olanzapine and aripiprazole treated rat group showed significant decrease in, body weight, liver weight, fasting blood glucose, triglyceride, and cholesterol level when compared to olanzapine treated rats (Table 3).

Combined olanzapine and aripiprazole treated group showed significant decrease in body weight when compared to olanzapine treated group. Similar results were found by Henderson *et al.* [86], who report the results of a 10-week placebo controlled, double-blind crossover study that examined 15 mg/day aripiprazole's effects upon multiple parameters including weight in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine. They found that, subjects experienced significant reductions in weight after the addition of aripiprazole to a stable dose of olanzapine. And that aripiprazole was well tolerated.

Combined olanzapine and aripiprazole treated rat group showed significant decrease in, liver enzymes and serum bilirubin level when compared to olanzapine treated rats (Table 3). Olanzapine treated rats had more significant increase in liver enzymes and serum bilirubin level when compared to control group and aripiprazole treated rats. This is in line with Gonzalez *et al.* [87] and Ozcanli *et al.* [88]. Atypical antipsychotic drugs commonly cause asymptomatic increase in the liver enzymes and serum bilirubin levels, but rarely cause serious hepatotoxicity [89]. There exists a single study on olanzapine-induced hepatotoxicity supplemented with the histopathological findings that reported no damage to the general architecture of liver except to hepatocytes at cellular level, using doses of 2 and 4 mg/kg/d i.p for six weeks [90]. Liver enzymes elevation has been, however, reported extensively, but asymptomatic and returned to normal when the drug was discontinued [87] [88]. On the other hand, Gomez and colleagues studied more than 2000 patients treated with olanzapine who exhibited no symptoms of jaundice or clinical hepatitis at six month follow-up [10].

The association of Non-Alcoholic fatty liver disease [NAFLD], and metabolic syndrome [MetS] has been previously reported [91].

The importance of linking olanzapine, metabolic syndrome and liver steatosis came from the recent finding of Ballestri *et al.* [20] that, NAFLD is considered the hepatic manifestation of metabolic syndrome [MetS].

Histological examination of liver in control group (**Figure 1**) shows the maintenance of normal lobular architecture, normal histology. Histopathological finding in olanzapine treated rat group (**Figure 3**) in the present study showed a picture of non-alcoholic liver disease in the form of ballooning degeneration, inflammatory infiltrates and accumulated lipid vacuoles in hepatocytes [steatosis] [8 rats]. Steatosis was predominantly microvesicular and found in more than 50% of the lobules. Many Kupffer cells were also present. It had larger total fat cell areas than the control. There was no significant portal inflammation or hepatocytes damage at aripiprazole treated rats (**Figure 2**). And the portal tract showed small aggregates of chronic inflammatory cells. Combined olanzapine- and aripiprazole-treated rats (**Figure 4**) showed less prominent and less severe picture of non-alcoholic liver disease [3 rats] compared to olanzapine treated rats [8 rats].

In a study by Chakrakodi *et al.* [92], they examined the effect of aripiprazole in therapeutic dose [TD] and maximum therapeutic dose [MTD] for a period of 8 weeks on the liver histopathology of adult Sprague-Dawley rats. There was no significant portal inflammation or hepatocytes damage at TD, but at MTD, the portal tract showed small aggregates of chronic inflammatory cells.

Soliman *et al.* [93] compared liver histopathological changes in adult male albino rats treated with either olanzapine or aripiprazole for 14 weeks. They found histopathological changes in the liver in the form of non-alcoholic fatty liver disease in both olanzapine treated group and aripiprazole treated group. And that, these changes were more prominent and severe in olanzapine treated group than in aripiprazole treated group.

There was a trend towards an association between NASH and metabolic syndrome; in addition, patients with NAFLD with MetS were more likely to have severe steatosis and portal inflammation on liver biopsy [94]. Non-alcoholic steatohepatitis [NASH], which is recognized as a progressive form of fatty liver disease, has been documented to have the potential to progress to cirrhosis and hepatocellular carcinoma [21] [22].

## 5. Conclusions and Recommendation

Olanzapine treatment was found to be associated with risk factors of metabolic syndrome clinically and experimentally and its hepatic manifestation of non-alcoholic fatty liver disease in wister rats. These represent major challenges in the treatment of schizophrenic patients, as they reduce compliance and contribute to increased cardiovascular and hepatic morbidity among patients especially our vulnerable hepatically and metabolically Egyptian patients.

Screening for and trying to minimize risk factors [including antipsychotic medication choice and use] should be a key priority in the multidisciplinary treatment of people with schizophrenia. Schizophrenic patients on olanzapine

therapy must be followed regularly regarding metabolic parameters, hepatic, cardiac and cerebrovascular morbidity, with urgent interference with early manifestations. It is recommended to check liver enzymes regularly for those patients kept on atypical antipsychotic drug [olanzapine]. It is also important not to ignore the signs of liver damage if one is currently taking olanzapine and signs such as jaundice, abdominal pain or discomfort should not be taken lightly while taking olanzapine.

The addition of aripiprazole in olanzapine-treated subjects with schizophrenia was well tolerated and did not result in a change of psychiatric symptoms. Improvements were observed clinically and experimentally on measurements that predict medical morbidity and mortality, including weight, fasting blood glucose, triglycerides and non-alcoholic fatty liver changes in rats.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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