Ultrastructure and Pathology Study of the Effect of an Antidepressant (Olanzapine) on the Health of Mitochondria in liver of male Albino Rat

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Abstract

**Background:** Depression is one of the most common diseases in the last period, and it is a psychological disease that affects different age groups. In a scientific study conducted in the United States, the prevalence of it was large and expected to spread in other countries, which made it a catalyst for many doctors to do many studies that depend on the effect of sedative drugs (Andrade L, et al., (2003)). Olanzapine is considered an anti-depressant medication and may have a direct impact on the body’s organs in general. Therefore, many studies have examined the harm of taking sedative drugs and the possibility of studying changes or side effects to them and the possibility of treatment where many studies indicated the impact of the liver by it, as the liver is the first organ in the process of filtering the body from toxins with fatty tissue.

**Methods:** The study was conducted on 50 male white rat (Albino rat) and divided into groups. The first group: (10) rats, the negative group that fed the standard meal, the second group: (10) rats, the treatment group that was given a dose of ZYPREXA at a rate of 6 mg/kg/day for eight weeks orally by the gastric tube. The dissection was carried out, a sample was taken from the liver and placed in the anthrax-stabilizer “primary stabilizer”, then placed in osmium and the steps followed for electronic microscopy were followed (Bancroft & Stevens, (1996)).

**Results:** When examining the micro-structural sectors of the liver tissue, pathological changes in the hepatic sectors appeared from their normal form, with blood stasis, bleeding and inflammation of the hepatic cells. Acute deformation of the hepatocytes and mitochondrial degeneration and change in its forms with the fragmentation of the rough endoplasmic reticulum and the abundance of the smooth endoplasmic reticulum, a large number of caper cells and phagocytic cells, hematuria, the emergence of collagen fibers and deformation in the portal area and bile ducts.

**Keywords:** Zyprex, Liver, Sinusoid, Kupffer cell, I to cell, hepatocytes

Introduction

Depression is a common disease these days and it is a mental illness that affects people of all ages and it is a very common disorder among the general public. In a scientific study conducted in the United States, it was found that the prevalence of the disease was 16.9%, and it is expected that it will spread in the world at higher rates which led many doctors of the International Epidemiology Federation to study the effect of sedatives as people treat them as a treatment for depression [1]. Antidepressants are known to have negative effects. The effects of antipsychotics on the second generation are high on metabolic syndrome and may have harmful side effects on body parts such as the liver. These are the filtration organs responsible for developing the effects of antidepressants. Medicines increase the production of sugar in the liver by activating adenosine and activating protein kinase in the hypothalamus in the brain, which activates the presence of Olanzapine, which leads to high blood sugar [2].
Materials and methods

Animals
- The study will be conducted on the males of the white rats (Albino rat) 20 Control Group: (10) the rats of the negative group who feed on the standard meal.
- The second Treatment group: (10) treated with Zyprex dose at 6 mg/kg/day for 8 weeks by mouth via stomach tube for four weeks by the gastric tube.

Chemicals
Drug: Zyprexa is used as an antidepressant Effect of black bean on the immune system: Studies and scientific research mention that the black bean has a stimulating effect on immune functions and this effect has been shown to improve the effectiveness of natural killer cells and these results can be of great therapeutic importance in the prevention of cancer, liver viruses and cases associated with deficiency in immune system.

Ultrastructure Studies
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Results
Control group (Figure 1-6).
Treatment Group (Figure 7-22).

Discussion
Olanzapine is an antidepressant, which has a strong effect on the liver when ingested, as previous studies have shown the occurrence of hepatitis, high blood lipids and sugar in the blood plasma. In this study, rat depression was treated with a dose of 6 ml/ kg body weight for eight weeks. Body weight was observed through the gastric tube based on previous studies and doses were given without depriving rats from food or water represented by the natural person taking doses of the medication on the group of treated rats. The results showed liver cell damage and increase in Kupffer cell count, which was confirmed [4]. Antidepressants have
positive effects on the liver in both male and female rats [5,6].

Therefore, this study aims to determine the effect of Olanzapine on the liver and its harmful effects.

Olanzapine (6 ml/kg body weight) was used in this study [7,8]. As agreed with SW Woods, [9]. Blood samples were taken from rats to examine blood sugar and lipids. This is an indication of hepatitis [10]. It was observed in patients taking olanzapine (weight gain, fat disorder, insulin resistance and hypertension).

Blood sugar as the transcription reflects a lower glucose metabolism rate. It is reported that olanzapine has a strong correlation with the emergence of new diabetes.

[11] Weight gain is one of the risk factors for diabetes. It was observed that when APDs were discontinued, plasma glucose was reduced [12,13].

[14,15] In animal models, anti-psychotic medications (APDs) have been shown to cause hyperthyroidism, leading to weight gain and high blood sugar [16].

[11] The group treated with Olanzapine:
The histological study of the liver of male rats treated with
olanzapine showed several different changes appearing in the composition of the liver cells due to the appearance of many cell necrosis, atrophy of nuclei and severe tissue abnormalities and widening of the sinuses, fluid runoff, vascular congestion, blood stasis, and increase of Kupffer cells was seen as a result of the severity of inflammation, cellular degradation and nuclei deny. Deformity and congestion of the portal artery are observed, the multiplication of the bile ducts and the severe damage to the liver cells; there was a sharp expansion of the hepatic artery, endothelial cell enlargement and liver cell decomposition. Central hepatic vein fibrosis has also been severely seen as a result of inflammation and blood stasis within it, hematuria, abnormal proliferation of bile ducts, hepatic artery enlargement, endothelial separation, inflammatory cell appearance, and some fat drops as evidenced [17]. The group treated with olanzapine showed...
fibrosis and seborrhea hepatitis, as large drops of fat were observed in the areas surrounding the nucleus and increased smooth network, as well as a large number of myelin fibers. He showed a marked increase in the level of cholesterol in the blood throughout the treatment period, and the results were significantly higher after the third week (44.69%) and this consistent with the results [18]. The deformation of the portal vein, the macrophage cell multiplicity, the severity of inflammation, enlarged nucleus, and hematogenesis are strongly observed within the central vein. Olanzapine causes pathological changes in the liver. A significant increase in body weight was observed throughout the treatment period, after the first week (55.87%). This is consistent with [19]. This is also consistent with the increase in body weight in the olanzapine group with a study [20]. There was a significant increase in the level of cholesterol throughout the treatment period, and the results recorded the highest significant increase after the
third week (44.69%), which corresponds to [21].

As [22] mentioned, olanzapine has been positively associated with weight gain, cholesterol and sugar. There was a clear increase in the expansion of the blood pockets and the increase in the Kupffer cells, the severity of inflammation and deformation in the form of irregular nuclei and chromatin, deformation of mitochondrial forms, hypo-density, diminishing numbers and the appearance of gaps within them, internal dissolution, degradation of the rough endoplasmic reticulum and bile duct deformation. Increased bile duct multiplication from the severity of inflammation, increased fat, increased myelin fibers, and the emergence of ITO cells to store fat, consistent with [17,22].

Pathological changes also show the shape of endothelial cells, Kupffer cells, nucleus irregularities, increased homogeneous chromatin masses, decreased electron density, heterogeneous chromatin, nucleation and nuclear abnormality, which reduce functional efficiency and deformation of the Golgiapparatus [23]. Cellular swelling and membrane damage have been detected. Programmed cell death occurs while the cell membrane remains intact.

Chronic olanzapine treatment results in a low-grade inflam-
Figure 20: Treatment Group.
A photograph of the electron microscope in a section of the liver of male rats showing blood stagnation (RBC) and Kupffer cells (K) inside the sinuses Blood (S) (X12000).

Figure 21: Treatment Group.
A photogrammetry of the electron microscope in force in a male liver. Rats analyzing and altering the shape of the nucleus (N), chromatin distribution, and decomposition of mitochondria (M) and glycogen assemblies (G) in the cytoplasm and coarse endoplasmic reticulum (RER). (X50000).

Figure 22: Treatment Group.
Photographic electron microscopy of in the liver of male rats showing the nucleus, including chromatin and nuclear poor (Np) and the presence of coarse endoplasmic reticulum (RER) and glycogen concentrations (G) X25000).

Conclusions
1. Olanzapine antidepressants, which are used to treat depression and psychosis, have harmful effects on the liver and weight gain.
2. Not to take too much antidepressants because they harm the liver.
3. Antidepressants increase blood sugar.

Competing interests
The authors declare that they have no competing interests.

Acknowledgement
I thank the University of Jeddah for providing the opportunity to conduct research in the Laboratories, Material support and help in the Dissemination of research as well as a continuous thanks to the scientific journal of histology and histopathology and thanks to King Faisal University in Dammam for the use and work of the electronic microscope sectors.

Publication history
Editor: Khin Thway, The Royal Marsden Hospital, UK.
Received: 04-Feb-2020 Final Revised: 16-Mar-2020
Accepted: 25-Apr-2020 Published: 21-May-2020
References

1. Albaugh VL, Henry CR, Bello NT, Hajnal A, Lynch SL, Halle B and Lynch CJ. Hormonal and metabolic effects of olanzapine and clozapine related to body weight in rodents. *Obesity (Silver Spring).* 2006; 14:36-51. | Article | PubMed Abstract | PubMed FullText

2. Ikegami M, Ikeda H, Ohashi T, Ohsawa M, Ishikawa Y, Kai M, Kamei A and Kamei J. Olanzapine increases hepatic glucose production through the activation of hypothalamic adenohypophysis-5'-monophosphate-activated protein kinase. *Diabetes Obes Metab.* 2013; 15:1128-35. | Article | PubMed

3. Hsu YC. *Theory and Practice of Lineage Tracing.* *Stem Cells.* 2015; 33:3197-204. | Article | PubMed Abstract | PubMed FullText

4. Todorovic N, Tomanovic N, Gass P and Filipovic D. Olanzapine modulation of hepatic oxidative stress and inflammation in socially isolated rats. *Eur J Pharm Sci.* 2016; 81:94-102. | Article | PubMed

5. Davey KJ, O'Mahony SM, Schellekens H, O'Sullivan O, Bienenstock J, Cotter PD, Dinan TG and Cryan JF. Gender differences in the effect of chronic olanzapine in rats: effects on body weight, inflammatory, metabolic and microbiota parameters. *Psychopharmacology (Berl).* 2012; 221:155-69. | Article | PubMed

6. Mallazadeh H and Hosseinzadeh H. The effective effect of Nigella sativa against liver injury: a review. *Iran J Basic Med Sci.* 2014; 17:958-66. | Article | PubMed Abstract | PubMed FullText

7. Pae CU, Lim HK, Kim TS, Kim JJ, Lee CU, Lee SJ, Lee C and Paik IH. Naturalistic observation on the hepatic enzyme changes in patients treated with either risperidone or olanzapine alone. *Int Clin Psychopharmacol.* 2005; 20:173-6. | Article | PubMed

8. Gulec M, Ozcan H, Oral E, Dursun O, Unal D, Aksak S and Albayrak A. Nephrotic effects of chronically administered olanzapine and risperidone in male rats. *Klinik Psikofarmakoloji Bületeni-Bulletin of Clinical Psychopharmacology.* 2012; 22:139-147.

9. Milano W, Grillo F, Del Mastro A, De Rosa M, Sanseverino B, Petrella C and Capasso A. Appropriate intervention strategies for weight gain induced by olanzapine: a randomized controlled study. *Adv Ther.* 2007; 24:123-34. | Article | PubMed

10. Houseknecht KL, Robertson AS, Zavadskis W, Gibbs EM, Johnson DE and Rollerna H. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology.* 2007; 32:289-97. | Article | PubMed

11. Liebert KA, Markowitz JS and Caley CF. New onset diabetes and atypical antipsychotics. *Eur Neuropsychopharmacol.* 2001; 11:25-32. | Article | PubMed

12. Kohlen I, Gampel M, Reddy L and Manu P. Rapidly developing hyperglycemia during treatment with olanzapine. *Ann Pharmacother.* 2008; 42:588-91. | Article | PubMed

13. Waage C, Carlsson H and Nielsen EW. Olanzapine-induced pancreatitis: a case report. *JOP.* 2004; 5:388-91. | PubMed

14. Koller EA, Cross JT, Doraiswamy PM and Malozowski SN. Olanzapine increases hepatic glucose production through the activation of hypothalamic adenohypophysis-5'-monophosphate-activated protein kinase. *Diabetes Obes Metab.* 2013; 15:1128-35. | Article | PubMed

15. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR and Wirshing WC. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 2000; 61:742-9. | Article | PubMed

16. de Leon J, Susce MT, Johnson M, Hardin M, Pointer L, Ruano G, Windemuth A and Diaz FJ. A clinical study of the association of antipsychotics with hyperlipidemia. *Schizophr Res.* 2007; 92:95-102. | Article | PubMed

17. Schaff Z and Nagy P. [Novel factors playing a role in the pathomechanism of diffuse liver diseases: apoptosis and hepatic stem cells]. *Orv Hetil.* 2004; 145:1787-93. | PubMed

18. Van Brunt DL, Gibson PJ, Ramsey JL and Obenchain R. Outpatient use of major antipsychotic drugs in ambulatory care settings in the United States, 1997-2000. *MedGenMed.* 2003; 5:16. | PubMed

19. Yamauchi T, Tatsumi K, Makinodan M, Kimoto S, Toritsuka M, Okuda H, Kishimoto T and Wanaka A. Olanzapine increases cell mitotic activity and oligodendrocyte-lineage cells in the hypothalamus. *Neurochem Int.* 2010; 57:565-71. | Article | PubMed

20. Su KP, Wu PL and Pariante CM. The effect of dietary supplementation of Nigella sativa L on serum lipid profile in rats. *Saudi Med J.* 2009; 30:893-6. | PubMed

21. Melkersson KJ, Hulting AL and Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry.* 2000; 61:742-9. | Article | PubMed

22. Kocyigit Y, Atamer Y and Uysal E. The effect of dietary supplementation of Nigella sativa L on serum lipid profile in rats. *Saudi Med J.* 2009; 30:893-6. | PubMed

Citation: Batarfi NM. Ultrastructure and Pathology Study of the Effect of an Antidepressant (Olanzapine) on the Health of Mitochondria in liver of male Albino Rat. *J Histol Pathol.* 2020; 7:3. http://dx.doi.org/10.7243/2055-091X-7-3