Histological Evaluation of the Role of Atypical Antipsychotic Drugs in Inducing Non-Alcoholic Fatty Liver Disease in Adult Male Albino Rats (Light and Electron Microscopic Study)

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Abstract. Many of atypical antipsychotic drugs are associated with adverse metabolic effects, including fatty infiltration of the liver. This study aimed at studying the histological evaluation of the role of atypical antipsychotic drugs (olanzapine and aripiprazole) in adult male albino rats. Sixty adult male albino rats were divided equally into three groups. Group I served as a control while groups II and III were treated with olanzapine and aripiprazole consecutively. Sections of the liver were examined by light and electron microscopy. A highly significant increase in the weight of rats in olanzapine- and aripiprazole-treated groups in comparison to the control group was noticed. On the other hand, there was a highly significant increase in body weight of the olanzapine group in comparison to aripiprazole. Olanzapine- and aripiprazole-treated rats showed highly significantly increased fatty infiltration of liver (steatosis) compared with the control group. However, the aripiprazole-treated group showed less steatosis compared with olanzapine. The mean non-alcoholic steatohepatitis scoring and fibrosis of the olanzapine group were highly significantly increased compared to the aripiprazole group. Ultrastructurally, liver from the olanzapine group showed large fat droplets in perinuclear region, between cisternae of the rough endoplasmic reticulum, and in the space of Disse. Large-sized mitochondria and myelin figures were seen. Although histopathological changes of the liver in the form of non-alcoholic fatty liver disease were more prominent in the olanzapine group, they were also evident in the aripiprazole group.

Introduction

An antipsychotic drug is a tranquilizing psychiatric medication primarily used to manage psychosis (including delusions or hallucinations, as well as disorders of thought), particularly in schizophrenia and bipolar disorder. Antipsychotics might also be used to counter psychosis associated with a wide range of other disorders, such as psychotic depression (Richard et al., 2008).

Antipsychotic drugs are increasingly used to treat non-psychotic disorders. For example, they are sometimes used to manage aspects of autism disorders and treatment-resistant depression (Naomi et al., 2007). Antipsychotics have also been increasingly used for cases of dementia in older people, and for various disorders and difficulties in children and teenagers. A survey of children with developmental disorder found that
16.5% were taking an antipsychotic drug, most commonly to alleviate mood and behavioural disturbances characterized by irritability, aggression, and agitation (Poushy et al., 2008).

Antipsychotic drugs are categorized based on their clinical efficacy and their side-effect profiles (Henderson et al., 2000). The first-generation (typical) antipsychotic drugs are effective against the positive symptoms of schizophrenia, but unfortunately they often induce highly unpleasant side effects, such as extrapyramidal side effects (EPS) and hyperprolactinaemia (Huang and Chen, 2005).

In addition to being equally effective as the first-generation drugs against the positive symptoms, the second-generation (atypical) drugs seem to have better effect on negative and cognitive symptoms (Meyer, 2002). A meta-analysis demonstrated that some atypicals (clozapine, olanzapine, risperidone) apparently showed better overall clinical efficacy than other atypical (ziprasidone, sertindole, quetiapine, remoxipride) and typical drugs (haloperidol). Unfortunately, several atypical drugs are associated with various metabolic disturbances, such as weight gain, hyperglycaemia and hypertriglyceridaemia. These metabolic adverse effects are of great concern since they increase the risk for obesity-related complications and death. They also reduce the patient compliance. It is therefore noteworthy that olanzapine, which is associated with considerable weight gain, was recently ranked as the most effective antipsychotic drug in terms of discontinuation rates (Haddad and Weck, 2004).

Aripiprazole (Abilify) acts as a partial dopamine agonist. Because of its separate mechanism of action it has been described as a third-generation antipsychotic drug (Keltner and Johnson, 2002). Aripiprazole is claimed to be effective against positive, negative and cognitive symptoms of schizophrenia, whereas EPS and metabolic adverse effects appear to be quite infrequent (Mir and Taylor, 2001; Stahl, 2001). Its mechanism of action is thought to reduce susceptibility to metabolic symptoms seen in some other atypical antipsychotics (Swainston and Perry, 2004). However, the extent to which these effects differ from other atypical antipsychotics is debated (Wahl and Ostoff, 2005).

Non-alcoholic fatty liver disease (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 (Brunt et al., 1999).

Non-alcoholic steatohepatitis (NASH), now recognized as a progressive form of fatty liver disease, has been documented to have the potential to progress to cirrhosis and hepatocellular carcinoma (Brunt et al., 1999; Giulio et al., 2001). NASH may be a leading cause of “cryptogenic cirrhosis” in which aetiologically specific clinical laboratory or pathological features can no longer be identified (Day and James, 1998).

Neither clinical evaluation nor laboratory values can ensure either the diagnosis or the exclusion of NASH, and liver biopsy interpretation continues to be considered the “gold standard” for the diagnosis (Brunt, 2001). Therefore, this study was carried out to evaluate the histological role of atypical antipsychotic drugs (olanzapine and aripiprazole) in inducing non-alcoholic fatty changes in the liver of adult male albino rats, especially because so far there has been no literature reporting this point.

**Material and Methods**

**Animal model**

Sixty adult male healthy Wistar albino rats (4 months old, weight 150–160 g), purchased from King Abd Al Aziz University Animal House, Jeddah, KSA, were used throughout the study. Rats were subjected for 10 days to controlled conditions of temperature, illumination and allowed free access to commercial rat chow, purchased from EL Nasr Pharmaceutical Chem. Co., New Maadi, Cairo, Egypt. Diet and water were left ad libitum. All experiments were carried out in accordance with the protocol approved by the local experimental ethical committee at Deanship of Scientific Research, Taibah University, Al Madina Al Monawarah, KSA.

**Experimental design of research**

Initial weight and waist circumference were measured at the beginning and end of the experiment for all rats. Regarding waist circumference, rats were placed in ventral position and the waist circumference was assessed in the largest zone of the rat’s abdomen using a plastic non-extensible measuring tape with an accuracy of 0.1 cm (Gerbaix et al., 2010). All experiments were carried out in accordance with the protocol approved by the local experimental ethical committee at Deanship of Scientific Research, Taibah University, Al Madina Al Monawarah, KSA.

Group I: served as control untreated rats. They were maintained in the previously described conditions for 14 weeks.

Group II: included rats which received olanzapine (Eli Lilly and Co., Indianapolis, IN). The drug was given at a dose of 0.5 mg/kg/day, according to the drug calculation formula (Center for Drug Evaluation and Research, 2002; Felici et al., 2002; Shannon et al., 2007). Each tablet contained 5 mg, was dissolved in 10 ml normal saline, and the rat received 1 ml/kg/day of the dissolved drug via gastric tube to ensure that no drug loss occurs (Mortimer, 2007; Silver et al., 2007).

Group III: included rats that received aripiprazole (Bristol Myer Squib Company, New York City, NY). The drug was given at a dose of 2 mg/kg/day, according to the drug calculation formula (Center for Drug Evaluation and Research, 2002; Felici et al., 2002; Shannon et al., 2007). Each tablet contained 20 mg, was dissolved in 10 ml normal saline, and the rat received...
1 ml/kg/day of the dissolved drug via gastric tube (Reynolds et al., 2002).

Collection of histopathological specimens

Animals were anaesthetized at the end of the experiment by intraperitoneal administration of sodium pentobarbital (Sigma Chemical Co., St. Louis, MO) at a dose of 60 mg/kg body weight in 0.9% NaCl (Rosa et al., 2005). Abdominal skin was properly shaved and disinfected with 5% iodine solution. A 10-cm incision at the midline of abdomen was performed using no. 15 blade (Aesculap AG and Co. KG, Tutlingen, Germany). The liver was taken from all rats and weighed. Half of the samples were processed for light microscopy and the other half of samples were processed for electron microscopy study.

Light microscopy processing

The specimens were fixed for a minimum of 24 h in 10% buffered formalin for all samples and then were processed through alcohol (70%, 90%, 100%) and embedded in wax using Leica automated tissue processor, model TP1050 (Leica Biosystems Nussloch GmbH, Nussloch, Germany). Sections were cut from each block, 5 µm in thickness. Sections were dewaxed with xylene and rehydrated through a descending alcohol series. Slides were stained with Harris’s haematoxylin and eosin (H&E) and Masson trichrome (Carleton, 1980; Bancroft and Stevens, 1996). All sections were examined and photographed using a light microscope (Olympus, U-MDOB, Olympus Optical Co. LTD, Tokyo, Japan) at Research Unit, Faculty of Medicine, Taibah University, Al Madina Al Monawarrah, KSA.

All liver biopsy specimens were examined. Scoring of necroinflammation and fibrosis was performed using the criteria devised by Brunt and Tiniakos (2005). NASH was diagnosed according to liver histology indicating steatosis (0–3): 1: <33 % of lobules, 2: 33–66 % of lobules and 3: >66 % of lobules with ballooning degeneration of hepatocytes (0–2): 1: mild or 2: marked, and lobular inflammation (0–3) based on observations of foci per 20x field: 1: 1–2 foci, 2: up to 4 foci, 3: >4 foci with total score 0–8. Fibrosis was assessed as the following criteria: stage 1: zone 3 perivenular, perisinusoidal/pericellular fibrosis, focal or extensive, stage 2: as above with focal or extensive perportal fibrosis, stage 3: bridging fibrosis, focal or extensive, and stage 4: cirrhosis.

Transmission electron microscopy processing (Glauret and Lewis, 1998)

Small liver specimens, 1-mm³, were fixed in 2.5% solution of glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) for 2 h and then post-fixed for 1–2 h in osmium tetroxide dissolved in the same buffer. Subsequently, they were dehydrated by passage through a graded ethan-ol series and in propylene oxide, and then embedded in epoxy resin. The embedded blocks were cut into semithin sections, 0.5 µm, and ultrathin sections, 70–90 nm, using an ultramicrotome. Toluidine blue was used to stain semithin section. Uranyl acetate and lead citrate were used for staining the ultrathin sections and these were studied by means of a JEOL 1010 electron microscope manufactured by JEOL Ltd Comp., Tachikawa, Tokyo, Japan at the Mycology and Regional Biotechnology Centre, Al Azhar University, Cairo, Egypt.

Statistical analysis

All data were expressed as mean ± SD. Statistical analyses were performed using IBM SPSS software version 19.00 (Chicago, Ill). One-way analysis of variance, pos-hoc, χ², t-test and least significant difference (LSD) were performed for inter-group comparison. P ≥ 0.05, P ≤ 0.05 and P ≤ 0.001 were considered non-significant, significant and highly significant, respectively (Dean et al., 2004).

Results

I. Measurement results

Regarding the mean body weight (/g), this study revealed a highly significant increase (P = 0.000) in the weight of rats between olanzapine and aripiprazole groups on one side and the control group on the other. There were highly significant differences (P = 0.000) in body weight in comparison between olanzapine and ari-
iprazole (Table 1).

Concerning mean waist circumference (/cm) the study showed a highly significant increase (P = 0.000) in waist circumference in comparing olanzapine with the control group. However, aripiprazole showed no significant increase (P = 0.10) when compared with the control group. Comparison between olanzapine and aripiprazole revealed a highly significant difference (P = 0.001) (Table 2).

Statistically, the mean liver weight revealed a highly significant increase in both olanzapine and aripiprazole.

Table 1. Means of body weight (/g) of all groups

<table>
<thead>
<tr>
<th></th>
<th>Mean body weight (/g)</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>P Values</th>
<th>Significance</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>279.45</td>
<td>5.98</td>
<td>1.3</td>
<td></td>
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<td>270.00</td>
<td>289.00</td>
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<tr>
<td>Olanzapine</td>
<td>401.65</td>
<td>7.58</td>
<td>1.6</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>390.00</td>
<td>415.00</td>
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<tr>
<td>Aripiprazole</td>
<td>307.400</td>
<td>9.13</td>
<td>2.04</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>295.00</td>
<td>324.00</td>
</tr>
</tbody>
</table>

*P was compared with the control group and #P was the comparison between olanzapine and aripiprazole. HS – highly significant
Table 2. Means of waist circumference (/cm) of all groups

<table>
<thead>
<tr>
<th></th>
<th>Mean waist circumference (/cm)</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>P Values</th>
<th>Significance</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15.270</td>
<td>1.8</td>
<td>0.42</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>11.0</td>
<td>17.50</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>18.605</td>
<td>2.1</td>
<td>0.49</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>16.00</td>
<td>23.50</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>16.375</td>
<td>2.2</td>
<td>0.49</td>
<td>*P = 0.10</td>
<td>NS</td>
<td>12.3</td>
<td>21.00</td>
</tr>
</tbody>
</table>

*P was compared with the control group and #P was the comparison between olanzapine and aripiprazole. HS – highly significant, NS – non-significant

Table 3. Means of liver weight (/g) of all groups

<table>
<thead>
<tr>
<th></th>
<th>Mean weight of liver (/g)</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>P Values</th>
<th>Significance</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.8</td>
<td>1.0</td>
<td>0.2</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>6.37</td>
<td>9.95</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11.9</td>
<td>2.2</td>
<td>0.5</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>7.00</td>
<td>15.78</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10.0</td>
<td>2.2</td>
<td>0.5</td>
<td>*P = 0.001</td>
<td>HS</td>
<td>5.00</td>
<td>13.06</td>
</tr>
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</table>

*P was compared with the control group and #P was the comparison between olanzapine and aripiprazole. HS – highly significant, S – significant

Fig. 1. Photomicrographs of liver sections from: A) control group showing central vein (CV) and hepatocytes (H) having acidophilic cytoplasm and vesicular nuclei arranged in hepatic cords around blood sinusoids (arrows), B) a few collagen fibres (arrows) surrounding the central vein and in the wall of blood sinusoids. Olanzapine-treated group showing: C) many hepatocytes having steatosis (arrows), D) thick periportal (curved arrow) and pericellular (thin arrow) collagen fibres surrounding ballooned hepatocytes, “chicken-wire fibrosis”, E) diffuse lobular mixed chronic (thin arrow) and acute inflammatory infiltrates with predominant neutrophils (thick arrow), F) fibrous bridging septa (arrows). Aripiprazole-treated group showing: G) many cells having mild steatosis (thin arrow), ballooning (thick arrow), and mixed lobular acute (yellow arrow) and chronic (white arrow) inflammations, H) persinusoidal fibrosis (arrows).
group (P = 0.000 and P = 0.001, respectively) when compared to the control group. Comparison between olanzapine and aripiprazole revealed a significant difference (P = 0.002) (Table 3).

II. Light microscopy results

Sections from the liver of the control group were formed of central veins as well as hepatocytes that had acidophilic cytoplasm and vesicular nuclei. They were arranged in hepatic cords around blood sinusoids. A few collagen fibres surrounding central veins and in the wall of blood sinusoids could be seen (Fig. 1, A, B).

Microscopic examination of the livers of the olanzapine-treated group showed many hepatocytes that accumulated lipid vacuoles (steatosis). Steatosis was predominantly microvesicular and found in more than 50% of the lobules. Many hepatocytes showed ballooning degeneration. Diffuse lobular mixed acute and chronic inflammatory infiltrates were seen, composed predominantly of neutrophils and lymphocytes. Many Kupffer cells were also detected. Masson trichrome stain showed focal to extensive perivenular/pericellular (“chicken wire”) fibrosis. Moreover, many cases showed periporal fibrosis and a few of them showed bridging fibrosis (Fig. 1, C, D, E, F). There was no cirrhosis.

Sections from the aripiprazole-treated group showed many cells that had mild steatosis (< 33% of lobules), mostly of microvesicular type. Ballooning degeneration was also detected. Lobules showed mild mixed acute and chronic inflammation. Masson trichrome stain showed perivenular/pericellular fibrosis in some cases. A few cases showed periporal fibrosis and a few others showed bridging fibrosis (Fig. 1, G, H).

### Table 4. The incidence of steatosis in different groups

<table>
<thead>
<tr>
<th></th>
<th>Steatosis +ve</th>
<th>Steatosis -ve</th>
<th>P Values</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>17</td>
<td>3</td>
<td>*P = 0.000</td>
<td>HS</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>11</td>
<td>9</td>
<td>*P = 0.000</td>
<td>HS</td>
</tr>
</tbody>
</table>

*P was compared with the control group and #P was the comparison between olanzapine and aripiprazole. HS – highly significant, S – significant

Both olanzapine- and aripiprazole-treated rats showed highly significantly increased (P = 0.000) liver steatosis compared with the control group (Fig. 1, A, C, E). However, the aripiprazole-treated group showed less steatosis compared with olanzapine (11/20 and 17/20, respectively, P = 0.04) (Table 4).

The mean NASH scoring of the olanzapine group was 5.4 ± 0.5 compared with 4.3 ± 0.8 for aripiprazole group. The difference was statistically highly significant (P = 0.000) (Table 5).

Regarding fibrosis, the difference was statistically significant (P = 0.025) between the olanzapine and aripiprazole group. All olanzapine-treated rats showed some degree of liver fibrosis. Most of them were of stage 2 fibrosis. On the other hand, four of aripiprazole-treated rats showed no fibrosis and most of examined samples were of stage 1 fibrosis (Table 6).

### Table 5. The mean NASH scoring of all groups

<table>
<thead>
<tr>
<th></th>
<th>Mean NASH Score</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>P Value</th>
<th>Significance</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5.4</td>
<td>0.5026</td>
<td>0.1124</td>
<td>*P = 0.000</td>
<td>HS</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>4.3</td>
<td>0.8013</td>
<td>0.1792</td>
<td>#P = 0.000</td>
<td>S</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

*P was the comparison between olanzapine and aripiprazole. HS – highly significant

### Table 6. The relation between different drugs and fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>P Value</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Olanzapine</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>#P = 0.025</td>
<td>S</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>#P = 0.025</td>
<td>S</td>
</tr>
</tbody>
</table>

*P was the comparison between olanzapine and aripiprazole. S – significant
The atypical antipsychotics (especially olanzapine) seem to cause weight gain more commonly than the typical antipsychotics. They also affect the metabolic disorders associated with weight gain including diabetes, which can be life-threatening (Hasnain et al., 2010).

As we found in the current study, olanzapine highly significantly increases body weight in comparison with the control. Previous studies have shown that olanzapine promotes fat accumulation in male rats by decreasing physical activity, repartitioning energy and increasing adipose tissue lipogenesis while impairing lipolysis (Vance et al., 2011).

It has been shown that not only the quantity of the fat mass, but also the fat mass distribution is important. The waist circumference reflects the visceral adipose tissue which is a cardio-metabolic risk factor (Gupta et al., 2007). In this study the waist circumference was also highly significantly increased in the olanzapine group compared with the control.

On the other hand, there are many controversies regarding weight problems while using aripiprazole. Extensive research has been conducted to answer the question whether aripiprazole causes weight gain or not. As a result of various studies, it has been concluded that the use of aripiprazole can lead to weight gain in a number of persons. However, some of the studies have also shown contradictory results. Some authors proposed that the mechanism of action of aripiprazole reduces susceptibility to metabolic symptoms seen in several other atypical antipsychotics (Swainston and Perry, 2004).

**Discussion**

Fig. 2. Electron micrographs of liver sections from: A) control group showing a hepatocyte with sharply demarcated rounded nucleus (N), many mitochondria (M), a few glycogen granules (thick arrow) and electron-dense cell membrane (thin arrow). B) Higher magnification of Fig. A showing a cell junction (thick arrow), lysosomes (L) and bile canalculus (B) containing microvilli (arrow). Olanzapine group showing: C) hepatocyte with large fat droplets in perinuclear region (arrows), D) electron-lucent material (curved arrow) inside glycogen granules and large-sized mitochondria (M), E) fat droplets (arrows) distributed between cisternae of rough endoplasmic reticulum, F) large-sized fat droplets in the space of Disse and cytoplasm of hepatocytes (arrows), collagen fibres (curved arrow) around blood sinusoids and neutrophils (N) inside sinusoids,Inset) myelin figure (curved arrow). Aripiprazole group showing: G) sharply demarcated rounded nucleus of a hepatocyte (N) and a few perinuclear lipid droplets (arrow), H) lysosome (L), glycogen granules (thick arrow), many mitochondria (M) and rough endoplasmic reticulum (arrow).

A, F, G × 8000; E × 6000; D × 25000; H × 15000; Inset × 10000
Food and Drug Administration (FDA) reported that in 4-6-week trials in adults with schizophrenia, there was a difference in the proportion of patients with weight gain [aripiprazole (8%) compared to placebo (3%)]. In a short-term, placebo-controlled trial in patients (6 to 17 years) with autistic disorder, the mean increase in body weight in the aripiprazole group was 1.6 kg vs. 0.4 kg in the placebo group [www.askapatient.com/viewrating.asp, 2009]. In the current study we found that aripiprazole significantly increased body weight compared with the control. However, olanzapine still caused higher significant increases in body weight in comparison to aripiprazole.

While studying NAFLD with regard to the manifestation of metabolic syndrome (Brunt et al., 1999; Brunt 2001), this work revealed that both olanzapine- and aripiprazole-treated rats showed highly significantly increased liver steatosis compared with the control group. However, the aripiprazole-treated group showed less steatosis compared with olanzapine. Also, the ultrastructural features of hepatocytes of both olanzapine- and aripiprazole-treated groups showed evidence of fat deposition, although it was more prominent in the olanzapine group.

Histological evaluation of liver sections remains a significant component for the diagnosis of steatohepatitis, as there are no specific diagnostic laboratory tests (Brunt, 2001). The histological features of steatohepatitis are distinct (Ludwig et al., 1997; Burt et al., 1998; Brunt 2001), and the types of inflammation and fibrosis generally do not overlap with the predominantly portal-based features of other chronic liver diseases (Brunt et al., 2003). These lesions include steatosis, mild mixed lobular acute and chronic inflammation, liver cell injury as manifested by ballooning degeneration of hepatocytes, and intra-acinar perisinusoidal fibrosis; the lesions in the non-cirrhotic liver often predominate in acinar zone 3.

In the current study in addition to steatosis, the affected liver of both olanzapine- and aripiprazole-treated rats showed evidence of hepatocyte injury, manifested by ‘ballooned’ hepatocytes, diffuse lobular mixed acute and chronic inflammatory infiltrate, predominantly neutrophils and sometimes with perisinusoidal fibrosis. This means that the lesion may be accepted as NASH. However, the mean NASH scoring of the olanzapine group was highly significantly greater than that of the aripiprazole group. This means that both groups had the potential of a progressive form of fatty liver disease, such as cirrhosis and hepatocellular carcinoma (Brunt et al., 1999; Giulio et al., 2001), although it was manifested to a lesser degree in the aripiprazole group.

In this study, we found evidence of fibrosis in both groups. All olanzapine-treated rats showed some degree of liver fibrosis, most of them of stage 2. On the other hand, four of aripiprazole-treated rats showed no fibrosis and most of the affected cases were of stage 1 fibrosis. There is extensive evidence supporting the role of oxidative stress-mediated lipid peroxidation in the progression of NAFLD from simple fatty infiltration of the liver (steatosis). Lipid peroxidation is an attractive candidate mechanism for NASH as lipid peroxidation products, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), potentially explain all of the histological features of NASH, including fibrosis. Studies in animal models of NAFLD have demonstrated clear evidence of increased reactive oxygen species production and lipid peroxidation. Further studies supported the link between simple fatty infiltration of liver (steatosis) severity, lipid peroxidation, and inflammatory cell infiltration of the liver (steatohepatitis) (Albano et al., 2005).

In conclusion, although metabolic side effects manifested as weight gain and NAFLD were more prominent in the olanzapine-treated group, they were also evident in the aripiprazole-treated group. We may therefore suggest that patients continued on aripiprazole therapy may be at increased metabolic risk. It is also important not to ignore the signs of liver damage if one is currently taking aripiprazole and signs such as jaundice, abdominal pain or discomfort should not be taken lightly while taking aripiprazole. It is recommended to check liver enzymes regularly for those patients kept on atypical antipsychotic drugs to avoid developing more liver complications.

**Acknowledgement**

There are no conflicts of interest.

**References**


