Original Article

Chronic Antidepressant Use: Effects on Various Organ Histology and Blood Cell Counts in Adult Albino Rats

Moses W. Bariweni, Yibala I. Oboma[1], Ebibodo Samuel[1]

Department of Pharmacology and Toxicology, Faculty of Pharmacy, [1]Department of Medical Laboratory Science, Faculty of Basic Medical Science, College of Medicine, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria

Abstract

Background: Chronic use of antidepressant drugs often results in drug-induced organ damage, which is mostly undetected and under-reported. The study aimed at evaluating the effect of selected antidepressants on organs and blood cell counts in adult albino rats. **Materials and Methods:** Adult rats were divided into four groups (n = 5): Group 1 (5 mL/kg of body weight/day normal saline), Group 2 (1 mg/kg of body weight/day risperidone), Group 3 (5 mg/kg of body weight/day fluoxetine), and Group 4 (15 mg/kg of body weight/day imipramine) for 14 days. The animals experienced different stressors during the treatment period to simulate physiological state of depression. On the 14th day, the animals were exposed to the forced swimming test 1 h after the respective treatments. On the 15th day, the animals were sacrificed under halothane anesthesia. Blood sample was collected. Liver and kidney were excised for histological examination. Results were analyzed using one-way analysis of variance. **Results:** Kidney histology was normal for all groups. Risperidone-exposed rats presented with hepatotoxicity with areas of zonal necrosis and partial central vein congestion. Neutrophil (%) was significantly reduced ($P < 0.01$) in all treatment groups when compared with controls. White blood cell count was significantly increased ($P < 0.01$) in the imipramine and risperidone treatment groups but significantly reduced ($P < 0.01$) in the fluoxetine treatment group when compared with controls. Also, the platelet count was significantly increased ($P < 0.01$) in the fluoxetine group but decreased in imipramine-and risperidone-treated groups. **Conclusion:** Chronic antidepressant use can cause changes in blood cell counts and drug-induced organ damage; hence, frequent organ function tests and blood count are required in patients undergoing chronic antidepressant therapy.

Keywords: *Antidepressant, fluoxetine, hepatotoxicity, histology, imipramine, risperidone*

Introduction

Depression is a recurrent neurotic disorder affecting all genders and ages and is a major world health burden.[1] Psychotropic drug abuse such as antidepressants, antipsychotics, sedatives, anxiolytics, and others cuts across all age groups.[2] Chronic utilization of these substances is a recurrent trend in medical practice as these conditions require long-term treatment to achieve resolution of symptoms howbeit with chances of relapse in some instances.[3] Prolonged use of antidepressant drugs tends to cause adverse effects even for the safest molecules. Drug-induced organ injury is a predominant challenge facing clinical practice.[4]

Studies conducted during clinical trials often do not portray the true outcome produced by drugs in actual clinical practice as they are often for a short duration and oftentimes, the numbers do not represent all categories of persons with real-life conditions.[5] The last few years have witnessed the advent of several newer antidepressant drugs with fewer adverse events than the classic agents such as tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors.[6] Antidepressant drug actions are not completely understood with etiologic factors such as oxidative stress being implicated as antidepressants may not all possess antioxidant activity.[7] Abnormalities in red blood cells (RBCs), mononuclear cells, and aerophilic stress markers in urine, cerebrospinal fluid, and postmortem brains have been reported with their use.[8-10] It is, however, strenuous to attribute kidney or liver impairment to a single medication in a patient.[11] Vis-à-vis drug-induced organ damage, antidepressants present a special clinical problem as many antidepressants are metabolized by hepatocytes and toxicity is then a concern. There are publications of hepatotoxicity linked to some antidepressants (e.g., sertraline, paroxetine, and nefazodone)

How to cite this article: Bariweni MW, Oboma YI, Samuel E. Chronic antidepressant use: Effects on various organ histology and blood cell counts in adult albino rats. J Rep Pharma Sci 2022;11:118-24.

Received: 25 Aug 2021
Accepted: 24 Apr 2022
Published: 29 Jun 2022

Address for correspondence:
Dr. Moses W. Bariweni, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria.
E-mail: mbariweni@yahoo.com, mbariweni@ndu.edu.ng

Access this article online

Website: www.jrpsjournal.com

DOI:10.4103/jrptps.JRPTPS_122_21

Quick Response Code:

in subjects without preexisting liver disease.[5] The impact of antidepressant drugs on liver integrity and progression of hepatic disease is largely unknown with no recommendations regarding liver function testing in patients taking antidepressant medication. Antidepressants though used extensively, the outcomes of therapy on hematologic and biochemical indices in patients were seldom evaluated unless symptoms of organ toxicity are visible. A need to establish a benchmark for blood and organ function evaluation in patients on antidepressants to avert preventable drug-related adverse effects exists. In this study, we evaluated hematological, biochemical, and histomorphologic changes in adult Wistar albino rats after chronic antidepressant therapy.

Materials and Methods

Experimental animals

Twenty (20) adult Wistar albino rats of both sexes weighing 150–250 g were obtained from the animal breeding and research unit of the institution. The rats were assigned into four groups and placed in eight accurately labeled cages (40 cm × 40 cm padded with wood shaving which was changed daily) with the males separated from the females in a ventilated room at ambient temperature for the 2 weeks' period of acclimatization. The rats were fed with mash hybrid feeds (Vital Feeds Ltd, Edo State, Nigeria) and water (ad libitum). Ethical approval (NDU/PHARM/PCO/AEC/38) dated February 12, 2020 was obtained from the Animal Ethics Committee of the study institution. All animals were handled in accordance with EU directive (2010/63/EU) for animals. This study was carried out between February and March 2021

Drugs

The following drugs are used: imipramine (Imi) (Recipharm Ltd, UK), risperidone (Risp) (Hangzhou Chemical Company Ltd, China), and fluoxetine (Flx) (Roche, Switzerland). All other reagents and chemicals used were of standard and were obtained from reputable companies. Risp was solubilized in 1% methanol and made up to volume with saline, and other drugs were soluble in saline.

Experimental protocol

The adult rats of both sexes were randomly assigned into four groups (n = 5). The control group was administered 5 mL/kg body weight/day of 0.9% normal saline daily for 14 days. Experimental groups 2–4 were administered 1 mg/kg body weight/day of Risp, 5 mg/kg body weight/day of Flx, and 15 mg/kg body weight/day of Imi for 14 days, respectively. Healthy non-pregnant animals were used, and treatments were administered by gavage once daily between 9 and 10 a.m. without blinding. The animals experienced different stressors (food or water deprivation on alternate days, cold water immersion for 10 min daily, isolation every 2 days) during the treatment period to simulate the physiological state of depression. On the 14th day, forced swimming test was conducted 1 hour after the respective treatments. The animals were sacrificed under halothane anesthesia on the 15th day, and blood sample was collected for hematological and biochemical analysis. Liver and kidney were excised for histological studies.

Forced swimming (Porsolt's) test

An open cylindrical container of 25 cm diameter and 25 cm height, filled with water at 25 ± 1°C to a depth of 15 cm,[12] was placed in an isolated environment devoid of noise during this experiment. Group 1 (placebo control) was administered 5 mL/kg body weight/day of 0.9% normal saline, Group 2 received 1 mg/kg body weight/day of Risp., Groups 3 and 4 were administered 5 mg/kg of body weight/day of Flx and 15 mg/kg of body weight/day of Imi, respectively. All treatments were administered orally for 14 days, respectively. One hour after the various treatments on the 14th day, each rat was exposed to the forced swim test in the cylinder. Time of inactivity (immobility time) was measured for the last 4 min within a 6-min test. A reduced time of inactivity was considered an antidepressant activity index.[13]

Histological assessments

On day 15, the rats were sacrificed under halothane anesthesia and the organs were excised, rinsed in normal saline, blotted with Whatman's number 1 filter paper, scrutinized for visible injury, weighed, and embedded in 10% formal saline. They were processed with a Leica TP 1020 tissue processor, embedded in pure paraffin wax using an embedding panel (Leica EG 1160), allowed to solidify and section using rotary microtome (Leica RM 2125). Enhanced pictures (×400) of hematoxylin and eosin (H & E)-stained tissue sections were produced using a digital microscope (Olympus®).

Hematological analysis

Blood samples were collected from the abdominal aorta of the rat under halothane anesthesia using a 2 mL syringe. The parameters measured include packed cell volume, white blood cell (WBC) count, RBCs, hemoglobin concentration (Hb), platelets count (PLT), neutrophil (NEU), and lymphocyte (LYM).

Biochemical assays

Biochemical assays [urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), and globulin (GL)] were performed in triplicates. The Fawcett and Scott 1960[14] and Brod and Sirota 1948[15] methods were utilized for urea and creatinine estimation. ALB concentration was determined as urea determination above.[16,17] TP and GL were estimated using the Biuret method.[18] The method of Reitman and Frankel (1957)[19] was employed for serum ALT and AST assays.

Statistics

Results were analyzed by one-way analysis of variance and Dunnet's *post hoc* test for multiple comparisons (GraphPad Prism version 6, San Diego, CA, USA). Data were considered

different at $P < 0.05$. Results are presented as mean ± standard error of mean (SEM) and "*n*" represents the number of animals per group.

Results

Effect of 14-day antidepressant administration on Porsolt's test in rats

Figure 1 represents the effect of antidepressant treatment on forced swimming test in rats. Risp significantly ($P < 0.001$) increased inactivity (floating) in rats, whereas Flx ($P < 0.0001$) and Imi ($P < 0.001$) significantly reduced floating time in rats vs. the sham-treated group (control).

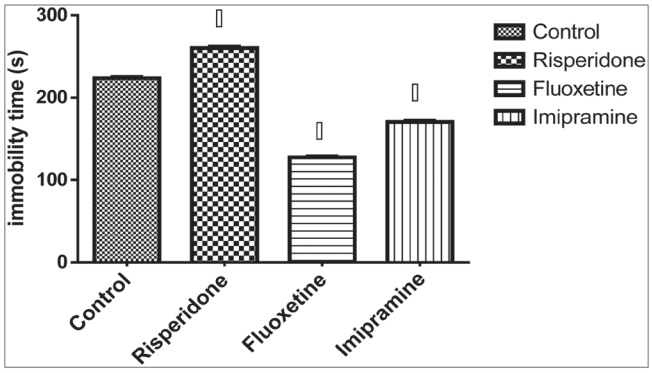

Figure 1: Effect of 14-day antidepressant treatment on forced swimming test in adult Wistar albino rats (α=*P* < 0.001, ß= *P* < 0.0001)

Alterations in liver and kidney histology of adult rats following 14-day antidepressant therapy

Changes in liver and kidney histology of adult rats following 14-day antidepressant administration are shown in Figure 2. Liver histology of the Risp-exposed rats shows areas of zonal necrosis and partial congestion of the central vein. The other treatment groups showed normal liver histological features. The kidney histology was normal for all groups [Figure 3].

Effect of 14-day administration of antidepressants on rat hematologic indices

Table 1 shows effects of antidepressants on rat hematological indices. NEU count was reduced ($P < 0.01$) in all treatment groups, WBC was significantly increased ($P < 0.01$) in the Imi and Risp treatment groups but significantly reduced ($P < 0.01$) in the Flx treatment group. No difference in RBC, LYM, MCV, and HB occurred between the groups.

Effect of 14-day therapy with antidepressants on rat biochemical indices

The data in Table 2 resulted from 14-day antidepressant therapy on biochemical indices of rats. ALT concentration was significantly elevated ($P < 0.01$) in the Flx- and Imi-treated groups vs. the saline group; also, the Flx and Imi treatment groups had elevated (both at $P < 0.01$) AST levels. Urea levels reduced ($P < 0.05$) in the Risp treatment group, but the ALT, AST, ALB, TPs, and creatinine levels were same with those of controls.

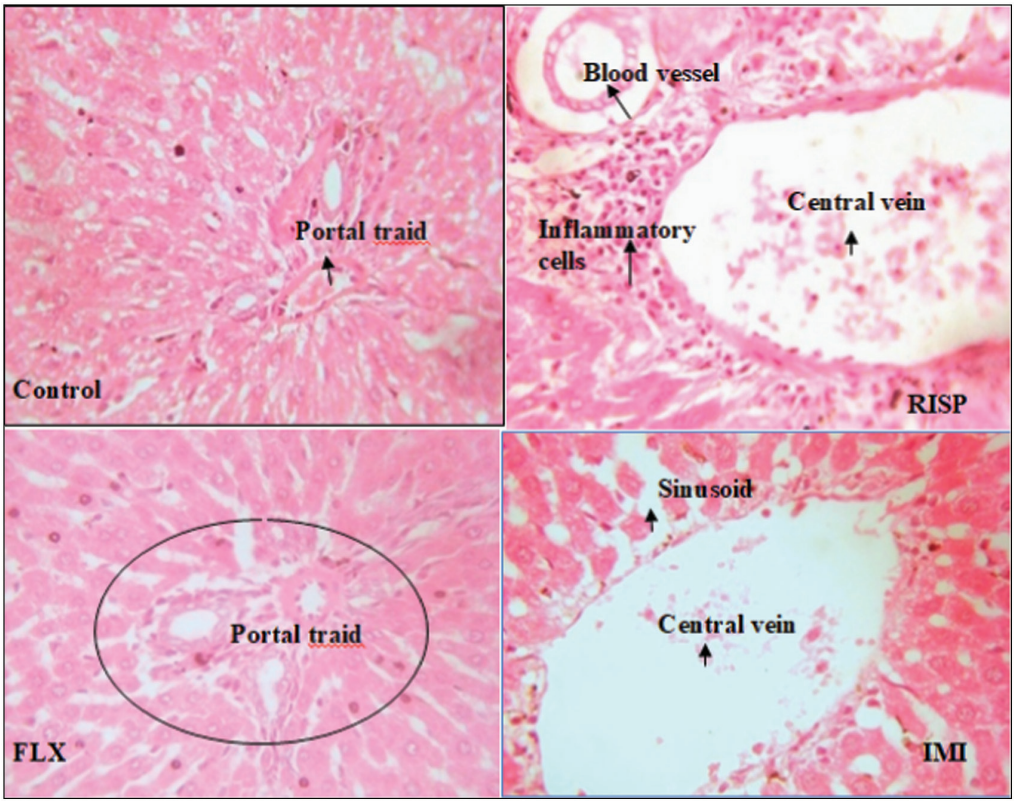

Figure 2: Photomicrograph of liver (400× H&E) exposed to normal saline (5 mL/kg body weight/day), Risp (1 mg/kg body weight/day), Flx (5 mg/kg body weight/day), and Imi (15 mg/kg body weight/day). The group administered with Risp shows areas of zonal necrosis and partial congestion of the central vein

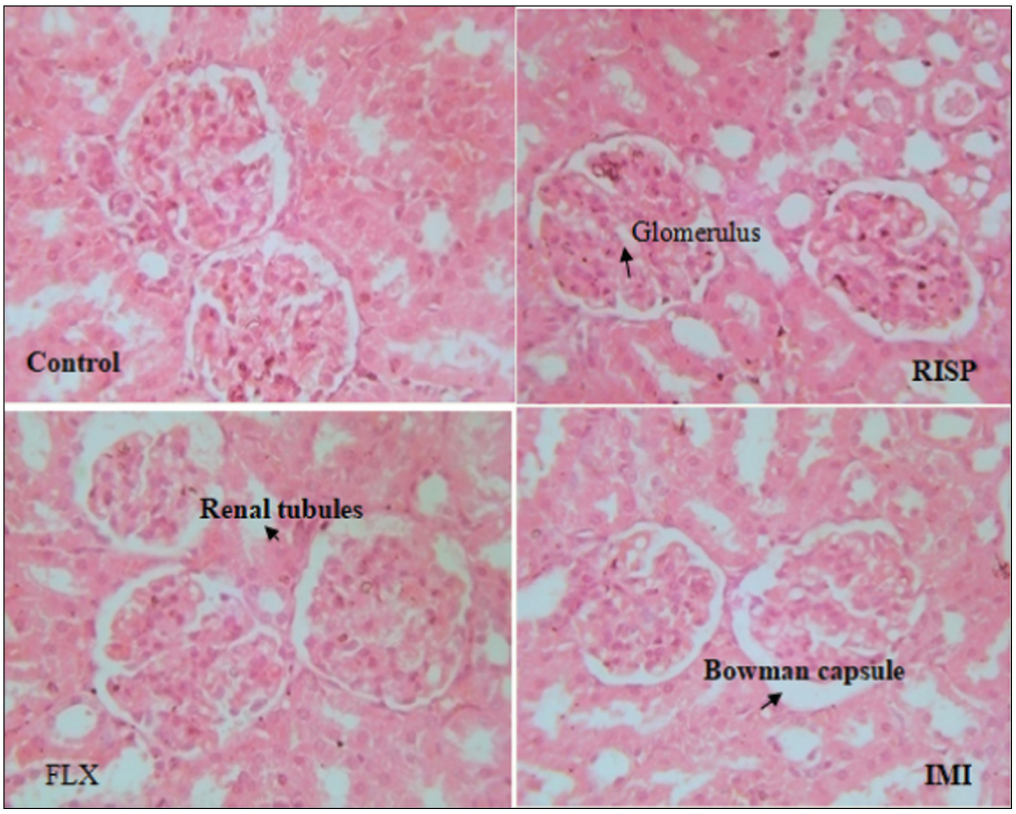

Figure 3: Photomicrograph of kidney (400× H&E). All treated groups show normal kidney histology (normal Bowman's capsule and glomerulus, normal renal tubules)

Table 1: Effect of 14-day administration of antidepressants on hematologic indices of rats

Parameter	Control	Imipramine	Risperidone	Fluoxetine
PLT (×10⁶/μL)	809.4±23.04	689.4±22.08**	799.4±38.13*	902.6±43.41*
WBC (×10⁶/μL)	9.3±0.31	12.9±0.31**	15.7±0.81**	7.9±0.25**
RBC (×10⁶/μL)	7.1±0.33	6.8±0.42	6.6±0.42	7.1±0.54
LYM (%)	44.4±1.73	46.2±1.84	51.2±1.84	53.0±2.15
NEU (%)	38.6±0.30	36.6±0.51	30.4±0.51**	24.0±1.58**
MCV (fL)	56.2±0.33	55.4±0.42	56.4±0.62	57.9±0.44
HB (g/dL)	12.7±0.33	11.8±0.42	12.4±0.67	12.1±0.46

*P < 0.05, **P < 0.01 vs. control. PLT: platelets, WBC: white blood cells count, RBC: red blood cells count, LYM: lymphocytes; NEU: neutrophils, MCV: mean corpuscular volume, HB: hemoglobin

Table 2: Effect of 14-day therapy with antidepressants on biochemical indices of rats

Treatment Parameter	Control	Imipramine	Risperidone	Fluoxetine
ALT (IU/L)	27.9±1.16	32.9±1.86	29.1±2.08	37.6±1.66**
AST (IU/L)	196.5±5.48	224.6±8.64*	289.8±7.99**	283.0±9.22**
Urea (IU/L)	37.0±0.26	38.2±0.86	35.6±0.44	36.7±1.02
Creatinine (mg/dL)	0.48±0.06	0.51±0.06	0.49±0.03	0.46±0.04
Albumin (mg/dL)	4.55±0.14	4.08±0.16	3.98±0.12	4.22±0.22
Globulin (mg/dL)	2.53±0.12	2.44±0.18	2.23±0.09	2.68±0.18
Total protein (mg/dL)	7.08±0.27	7.02±0.14	6.88±0.18	6.57±0.18

*P< 0.05, **P<0.01 compared with control. ALT: alanine aminotransferase, AST: aspartate aminotransferase

Discussion

In Porsolt's test, the inactivity time depicted in the Risp group is not a classical feature of antidepressant drugs. Risp treats schizophrenia, bipolar depression, and irritability linked to autism.[20] Treating depression with antidepressant therapy may relieve some but not all symptoms, in such cases Risp is sometimes used as a complement in depression resistant to other therapies.[21] Dhir and Kulkarni[22] also reported that Risp potentiated the anti-immobility actions of venlafaxine and Flx in the forced swim test but had no effect on its own. This is in agreement with the findings in our present study. This may be connected with its mode of action as it also inhibits both D_2 and $5HT_2$ receptors. Enhancement of 5HT transmission promotes swimming behavior[23]; therefore, its inhibitory action on $5HT_2$ receptors may have contributed to its negative effect on the swimming behavior of the rats.

Liver function integrity can be evaluated by various means; measurement of liver enzyme concentrations in serum is a primary method of studying such effects. The most precise index of hepatotoxicity is ALT because it is mainly synthesized within the liver. AST is abundant in various tissues.[24] The increase in ALT and AST in our result agrees with that of Abdel Salam *et al*.[6] Serum concentrations of the aminotransferases (ALT and AST) elucidate the cellular integrity of hepatic tissue. An elevation in serum AST and ALT is due to alteration of structural integrity or secretory function of hepatocytes. The increase in AST and ALT is a classical sign of hepatotoxicity,[24] even though histological damage occurred only in the Risp-treated group. Risp (3 mg/kg) induced increase in reactive oxygen species generation, glutathione synthase depletion, lysosomal leakage, and lipid peroxidation in rats.[25,26] Antidepressants have been reported to increase peroxidation and diminish nitric oxide concentration in the liver.[6] Antidepressants modulate oxidative function in glial cells by a dose-dependent inhibition of nitric oxide production,[27] and this may culminate in oxidative stress and consequent toxicity. Acute studies with antidepressants reveal that they may possess antioxidant effects; however, these effects are reversed following chronic use and lead to hepatotoxicity in rats.[28,29] These pro-oxidant and antioxidant effects seem to be organ-specific as they tend to portray antioxidant effects in the blood but pro-oxidant effects in the liver,[28] and this may account for the results in this study.

Hematological analysis, a key diagnostic tool of disease conditions, reveals the balance between wellness and the morbid state of toxicological study participants.[24] WBCs are the first to be mobilized in immune reactions. A major activator of the defensive system in living tissues is the NEU; they are recruited in microbial infections and also mobilized in acute inflammation.[30] Thus, the significant decrease in neutrophil level elicited by the antidepressants is associated with suppression of free radical species generation.[6] The neutropenia seen in this report agrees with that of some other researchers.[28,31] Thrombocytopenia and granulocytosis manifested in the Risp- and Imi-exposed animals, whereas thrombocytosis and agranulocytosis were seen in the Flx-treated group. The difference in their hematologic effects may reflect their action modes. Flx, an antidepressant, mediates serotonin reuptake into presynaptic terminals, thus enhancing and prolonging serotonergic neurotransmission. The action mode for Risp is poorly understood. New frontiers mainly probe its propensity to block D2 and 5-HT2A receptors.[32] The TCA, Imi, owes its antidepressant activity primarily to suppression of noradrenaline and serotonin reuptake.[33] Neutropenia-associated thrombocytosis has been described in patients receiving mirtazapine, an atypical antidepressant.[31] This is in consonance with our findings except in the Flx-treated group in which thrombocytosis occurred. The elevated PLT predisposes patients to hemostatic disorders and consequent cardiovascular risk; these call for caution in utilization of these agents.

Cases of life-threatening hepatic and renal injury are reported in patients treated with antidepressant and antipsychotic medications.[6] The liver, a major organ of detoxification, is highly prone to chemical injuries.[34] The hepatic necrosis reported in this study resembles an acute, toxic injury to the liver. The time of onset of acute hepatic necrosis is typically short usually 1–14 days.[35] Widely reported drugs causative of hepatotoxic agents include acetaminophen, aspirin, cocaine, and others. In this report, rats treated with Risp exhibited hepatotoxicity with zonal necrosis and partial congestion of the central vein. Guicciardi *et al*.[36] reported that a severe form of hepatic injury can evolve into an acute or chronic liver failure, displaying features of cellular swelling with lysed cells, spilling intracellular content into the surrounding environment and ultimately eliciting an inflammatory response. The histomorphological observation in this report is not in line with previous studies of Mustafa *et al*.,[37] as they reported no hepatic architectural variations in adult rats administered with 2.5 mg/kg Risp orally for 3 weeks. Other animals exposed to Imi, Flx, and saline revealed features consistent with normal hepatic tissue architecture.

The glomerulus shows normal Bowman's capsule, and loop of Henle and both proximal convoluted tubules are with normal epithelium, showing that the drugs administered at the present concentration, dosage, and time are not nephrotoxic. Halici *et al*.[38] reported normal glomeruli with intact structure and blood perfusion in animals treated with Risp; this agrees with the present report. Our findings differ from those of Mustafa *et al*.,[37] which report the presence of histopathological abnormalities. However, they report that there is no strong evidence pointing to nephrotoxic effects of the antidepressants used in their study, although oxidative stress is suspected to have caused the histopathological changes seen in the study. We can hypothesize from our findings that antidepressant drug-induced toxicity may be more pronounced in some organs than others.

Conclusion

The present study showed that NEU count was reduced by Imi, Risp, and Flx; PLT count and WBC count were reduced by Imi and Risp. Flx increases PLT count. There was no harmful effect on kidney histology, except Risp-induced hepatic injury. Flx increased PLT. In conclusion, the antidepressants utilized in this research are capable of causing organ damage following chronic use; therefore, they should be used with caution.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. Nat Rev Neurosci 2006;7:137-51.
2. Duru C, Oluoha U, Okafor C, Diwe K, Iwu A. Socio-demographic determinants of psychoactive substance use among students of tertiary institutions in Imo State, Nigeria. J Addict Res Ther 2017;8:345.
3. Tiffany ST, Friedman L, Greenfield SF, Hasin DS, Jackson R. Beyond drug use: A systematic consideration of other outcomes in evaluations of treatments for substance use disorders. Addiction 2012;107:709-18.
4. Alomar M. Factors affecting the development of adverse drug reactions. Saudi Pharmaceut J 2014;22:83-94.
5. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: A review for clinicians. Am J Psychiatry 2014;171:404-15.
6. Abdel Salam OM, Mohammed NA, Sleem AA, Farrag AR. The effect of antidepressant drugs on thioacetamide-induced oxidative stress. Eur Rev Med Pharmacol Sci 2013;17:735-44.
7. Maes M, Ruckoanich P, Chang YS, Mahanonda N, Berk M. Multiple aberrations in shared inflammatory and oxidative and nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:769-83.
8. Moreno-Fernández AM, Cordero MD, Garrido-Maraver J, Alcocer-Gómez E, Casas-Barquero N, Carmona-López MI, *et al*. Oral treatment with amitriptyline induces coenzyme Q deficiency and oxidative stress in psychiatric patients. J Psychiatr Res 2012;46:341-5.
9. Rybka J, Kędziora-Kornatowska K, Banaś-Leżańska P, Majsterek I, Carvalho LA, Cattaneo A, *et al*. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. Free Radic Biol Med 2013;63:187-94.
10. Voican CS, Martin S, Verstuyft C, Corruble E, Perlemuter G, Colle R. Liver function test abnormalities in depressed patients treated with antidepressants: A real-world systematic observational study in psychiatric settings. PLoS One 2016;11:e0155234.
11. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 2000;356:1667-71.
12. Porsolt RD, Le Pichon M, Jalfre M. Depression: A new animal model sensitive to antidepressant treatments. Nature 1977;266:730-2.
13. Zomkowski ADE, Santos ARS, Rodrigues ALS. Involvement of opioid system in the agmatine antidepressant-like effect in the forced swimming test. Neurosci Lett 2005;381:279-83.
14. Fawcett JK, Scott JE. A rapid and precise method for the determination of urea. J Clin Pathol 1960;13:156-9.
15. Brod J, Sirota JH. The renal clearance of endogenous "Creatinine" in man. J Clin Invest 1948;27:645-54.
16. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with Bromcresol green. Clin Chim Acta 1971;31:87-96.
17. Grant GH, Silverman LM, Christenson RH. Amino acids and proteins. In: Tietz NW, editor. Fundamentals of Clinical Chemistry. Philadelphia: WB Saunders; 1987. p. 328-9.
18. Tietz NW. Clinical Guide to Laboratory Tests. 3rd ed. Philadelphia: WB Saunders; 1995. p. 13-6.
19. Reitman S, Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol 1957;28:56-63.
20. Kasper S, Montagnani G, Trespi G, Di Fiorino M. Treatment of depressive symptoms in patients with schizophrenia: A randomized, open-label, parallel-group, flexible-dose subgroup analysis of patients treated with extended-release quetiapine fumarate or risperidone. Int Clin Psychopharmacol 2015;30:14-22.
21. Fournier JC Robert J, Jan F. Antidepressant drug effects and depression severity. JAMA 2010;303:47-53.
22. Dhir A, Kulkarni SK. Risperidone, an atypical antipsychotic enhances the antidepressant-like effect of venlafaxine or fluoxetine: Possible involvement of alpha-2 adrenergic receptors. Neurosci Lett 2008;445:83-8.
23. Sharma HS, Sharma A. Amine precursors in depressive disorders and the blood–brain barrier. In: Riederer P, Laux G, Nagatsu T, Le W, Riederer C, editors. NeuroPsychopharmacotherapy. Cham: Springer; 2021. https://doi.org/10.1007/978-3-319-56015-1_423-1.
24. Bariweni WM, Yibala IO, Ozolua RI. Toxicological studies on the aqueous leaf extract of *Pavetta crassipes* (K. Schum) in rodents. J Pharm Pharmacogn Res 2018;6:1-16.
25. Aziz E, Eltham A, Yadollah A, Alireza P, Hamed H, Mohammad A. *In vitro/vivo* studies towards mechanisms of risperidone-induced oxidative stress and the protective role of coenzyme Q10 and N-acetylcysteine. Toxicol Mech Methods 2016;26:520-8.
26. Nevena T, Jelena Đ, Snežana P, Neda Đ, Snežana B. Antidepressants- and antipsychotics-induced hepatotoxicity. Arch Toxicol 2021;95:767-89.
27. Lee CH, Park JH, Yoo KY, Choi JH, Hwang IK, Ryu PD, *et al*. Pre- and post-treatments with escitalopram protect against experimental ischemic neuronal damage via regulation of BDNF expression and oxidative stress. Exp Neurol 2011;229:450-9.
28. Krass M, Wegener G, Vasar E, Volke V. The antidepressant action of imipramine and venlafaxine involves suppression of nitric oxide synthesis. Behav Brain Res 2011;218:57-63.
29. Inkielewicz-Stępniak I. Impact of fluoxetine on liver damage in rats. Pharmacol Rep 2011;63:441-7.
30. Ramsingh D. The assessment of the chronic toxicity and carcinogenicity of pesticides. In: Irving, editor. Krieger Robert Hayes' Handbook of Pesticide Toxicology. 3rd ed. Amsterdam: Elsevier; 2010. p. 2319-42.
31. Toprak SK, Erdogan E, Azap OK. Mirtazapine-induced thrombocytopenia and neutropenia. Turk J Hematol 2012;29:297-8.
32. Guzman F. Mechanism of Action of Risperidone. Psychopharmacology Institute; 2019. Available from: https://psychopharmacologyinstitute.

com/publication/mechanism-of-action-of-Risperidone-2126 [last accessed on March 23, 2021].
33. DeBattista C. Antidepressant agents. In: Katzung BG, Trevor AJ, editors. Basic and Clinical Pharmacology. 13th ed. London: Lange, McGraw-Hill Education; 2012. p. 520.
34. Richa S, Rajbala S. Chemical induced liver injury: Types, mechanisms and biomarkers. Anatom Sci 2018;1. article ID: 903. doi:10.24294/as.v1i3.903
35. Bethesda MD. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]: National Institute of Diabetes and Digestive and Kidney Diseases. Acute Hepatic Necrosis. [Updated May 4, 2019]. 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548560/ [last accessed on February 8, 2022].
36. Guicciardi ME, Malhi H, Mott JL, Gores GJ. Apoptosis and necrosis in the liver. Compr Physiol 2013;3:977-1010.
37. Mustafa G, Halil O, Elif O, Onur BD, Deniz U, Selina A. Nephrotoxic effects of chronically administered olanzapine and risperidone in male rats. Bull Clin Psychopharmacol 2012;22:139-47.
38. Halici Z, Keles ON, Unal D, Albayrak M, Suleyman H, Cadirci E, *et al*. Chronically administered risperidone did not change the number of hepatocytes in rats: A stereological and histopathological study. Basic Clin Pharmacol Toxicol 2008;102:426-32.