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Hematological and Biochemical Effects of some Antidepressants and Antipsychotics on Albino Rats

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ABSTRACT

Antidepressants and antipsychotics are among the most frequently prescribed classes of psychotropic medications, while these agents have significantly improved psychiatric care, they are also associated with a variety of side effects. The aim of the present study is to demonstrate the adverse effects of some antidepressants (Amitriptyline and Escitalopram) and antipsychotics (Clozapine) on hematological and biochemical parameters, including, kidney function in male albino rats. The rats were divided into seven groups. (G1), the control group, was given 1 ml/kg of saline solution. (G2) was given (low) dose of Amitriptyline (0.08 mg/kg). (G3) was given the high dose of Amitriptyline (0.25 mg/kg). G4 was given (low) dose of Escitalopram (0.03 mg/kg). G5 was given the high dose of Escitalopram (0.1 mg/kg). (G6) was given (low) dose of Clozapine (0.08 mg/kg). G7 was given the high dose of Clozapine (0.25 mg/kg). After a month, the results showed that the low doses of Amitriptyline and clozapine had non significant changes in total WBCs counts, neutrophils, monocytes and lymphocytes counts, but, the high doses of these drugs induced significant decrease in these parameters. The low and high doses of Escitalopram induced non significant changes in these parameters and in Erythrocytes counts, Hemoglobin, Platelets, PCV, MCV, MCH, MCHC, RDW, Creatinine, Blood Urea, Uric Acid, Total Testosterone, Cholesterol, Triglycerides, LDL-C, HDL-C, VLDL, HDL, GGT, Total Protein, Albumin, A/G Ratio and NO. The low and high doses of Amitriptyline and clozapine induced significant increase in Creatinine, Blood Urea, Uric Acid, GGT, Cholesterol, Triglycerides, LDL-C, VLDL, and significant decrease in Erythrocytes count, Hemoglobin, Platelets, PCV, MCV, MCH, MCHC, RDW, Total Testosterone, HDL-C, Total Protein, Albumin, A/G Ratio and NO. Conclusion: The present results showed severe side effects of administration of Clozapine and Amitriptyline to rats represented in disturbance in hematological parameters and blood functions, toxicity in kidney functions, in addition to, toxic effects of these drugs concerning sex hormones, while, administration of Cipralex did not induce adverse effects in most of the mentioned parameters.

Keywords: Hematological parameters, Kidney function, Testosterone, Amitriptyline, Escitalopram, Clozapine.

1. Introduction

Psychiatric disorders such as depression, anxiety, and schizophrenia are among the most disabling conditions worldwide, requiring long-term pharmacological interventions for symptom control and improved quality of life. Among the wide range of psychotropic agents available, Amitriptyline, Clozapine, and Escitalopram represent important therapeutic options, each with distinct mechanisms of action and clinical applications (Lochmann & Richardson, 2019).

Amitriptyline (Tryptizol), is a tricyclic antidepressant (TCA) widely used in the management of depression and various associated psychiatric and somatic conditions. It exerts its therapeutic effects by inhibiting the reuptake of key neurotransmitters (serotonin and norepinephrine) and improving mood regulation. Escitalopram (Cipralex) is a selective serotonin reuptake inhibitor (SSRI) widely prescribed for depression and various anxiety disorders, including generalized anxiety disorder, panic

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disorder, and social anxiety disorder. It enhances serotonergic transmission in the brain, thereby improving mood regulation and reducing anxiety symptoms. (Kennedy et al., 2009). Clozapine, an atypical (second-generation) antipsychotic, is considered the gold standard for treatment-resistant schizophrenia. It exerts its effects through antagonism of dopamine D2 and serotonin 5-HT2A receptors, which contributes to its superior efficacy in reducing psychotic symptoms and suicidal behavior (Meltzer, 2012).

While these agents have significantly improved psychiatric care and patient outcomes, they are also associated with a variety of side effects including, gastrointestinal disturbances, metabolic syndrome, dyslipidemia, insulin resistance, and increased risk of type 2 diabetes, weight gain or loss, insomnia or sedation, sexual dysfunction, and increased risk of bleeding. Tricyclic antidepressants are also associated with cardiovascular side effects, orthostatic hypotension, and potential drug–drug interactions. (Campforts *et al*., 2023; Carli *et al*., 2021).

Antidepressants, particularly selective serotonin reuptake inhibitors are generally considered safe, but evidence suggests potential associations with hyponatremia, acute kidney injury (AKI), and electrolyte imbalance. Tricyclic antidepressants have also been reported to affect renal function indirectly through hemodynamic changes and nephrotoxic drug interactions (Khanam *et al*., 2016). Moreover, elderly patients and those with pre-existing chronic kidney disease (CKD) are more vulnerable to such adverse effects. Also, antipsychotics, especially second-generation agents, have been linked to metabolic syndrome, diabetes, and cardiovascular complications, all of which can increase the risk of chronic kidney disease. (Lally & MacCabe, 2015).

Antidepressants, particularly (TCAs) and (SSRIs), have been associated with hematological side effects such as thrombocytopenia, leukopenia, agranulocytosis, and increased bleeding risk due to serotonin's role in platelet aggregation (Halperin & Reber, 2007). SSRIs have been shown to impair platelet function, thereby predisposing patients to abnormal bleeding, especially when combined with anticoagulants or non-steroidal anti-inflammatory drugs. Antipsychotics, especially clozapine, are well known for causing serious hematological complications, most notably agranulocytosis and neutropenia, which necessitate routine blood monitoring during treatment (Meyer *et al*., 2015). Other antipsychotics have also been implicated in inducing anemia, eosinophilia, and leukocytosis (Laporte *et al*., 2017)

This research aimed to investigate and compare the safety and adverse effects of Amitriptyline, Clozapine, and Escitalopram on kidney functions and hematological and lipid profile parameters and testosterone levels in male albino rats.

2. Materials and Methods

2.1. Experimental animals

In this investigation, fifty-six male albino rats of the Sprague Dawley strain, weighing between 150 and 170 grams, were employed. The rats were acquired from the Faculty of Agriculture's Crops Department in Minia, Egypt. In accordance with Helsinki standards, the study protocol was accepted by the animal ethics committee of the Minia University Faculty of Science's Zoology Department. The guidelines for handling and caring for lab animals were adhered to. The rats were kept in clean, well-ventilated cages with a 12-hour light/dark cycle, a temperature-controlled room at 25°C, regular humidity, and commercial rodent food and water for two weeks to help them adjust.

2.2. Chemicals

Rats were made poisonous by using 99 percent pure amitriptyline. The group receiving a therapeutic low dose of amitriptyline was given a concentration of 0.08 mg/mL, which was prepared by dissolving sixteen 25 mg tablets in 300 milliliters of saline. We also prepared a high dose of amitriptyline by dissolving sixteen 25 mg tablets in 100 milliliters of saline, which produced a concentration of 0.25 mg/mL. The amitriptyline was purchased from "Outpatient Pharmacy." In order to prepare the therapeutic low dose of escitalopram, we dissolved forty 10 mg tablets in 300 milliliters of saline to create a concentration of 0.03 mg/mL. For the high dose, we dissolved forty 10 mg tablets in 100 milliliters of saline to create a concentration of 0.1 mg/mL. The tablets were purchased from "Outpatient Pharmacy." Twelve 25 mg tablets of Clozapine were dissolved in 300 milliliters of saline to create a concentration of 0.08 mg/mL, which was utilized for the group receiving a therapeutic low dose of Clozapine. Twelve 25 mg tablets were dissolved in 100 milliliters of saline to create a

concentration of 0.25 mg/mL for the high dose of Clozapine.

All the other chemical reagents and kits used in the study were of standard analytical grades and purchased from Sigma Chemical Co. (St. Louis, O, USA).

2.3. Experimental design

After the adaptation period, the rats were divided into seven groups (n=8 in each group) as follow:

Group 1: considered as the control group of eight rats which were given 1 ml/kg of saline solution (0.9 % Nacl) orally and once daily for a month.

Group 2: served as the low dose of Amitriptyline group in which rats were given orally therapeutic dose of Amitriptyline (0.08 mg/kg) once daily for a month.

Group 3: rats in this group received a three-fold therapeutic dose (high) of amitriptyline (0.25 mg/kg) orally once daily for a month. This group was known as the high dose of amitriptyline.

Group 4: was the low-dosage escitalopram group, where rats received a monthly oral therapeutic dose of escitalopram (0.03 mg/kg).

Group 5: rats in this group received a three-fold therapeutic dose (high) of escitalopram (0.1 mg/kg) orally once daily for a month. This group was known as the high dose of escitalopram.

Group 6: rats in this group received a therapeutic oral dose of Clozapine (0.08 mg/kg) once day for a month. This group was the low dose of Clozapine.

Group 7: rats in this group received a three-fold therapeutic dose (high) of Clozapine (0.25 mg/kg) orally once daily for a month. This group was known as the high dose of Clozapine.

2.4. Hematological and biochemical analysis

Animals were given unrestricted access to water but fasted for the whole duration of the trial. After the animals were killed while sedated with diethyl ether, two blood samples were taken right away. For plasma separation, the first sample was taken in a heparinized tube containing 2.25µ heparin and 5 ml blood. The second sample was taken in a non-heparinized tube so that the serum could be separated. Both tubes were centrifuged at 3000 rpm for 15 minutes in order to estimate several biochemical and hematological characteristics. Utilizing an automatic cell counter Micros ABX (Roche Diagnostic System, Montpellier, France), hematological parameters were ascertained. The following hematological parameters were examined: platelet count, erythrocyte count, hematocrit, and hemoglobin. The following differential count parameters were examined: leukocyte, neutrophil, lymphocyte, and monocyte counts (Casacó *et al.*, 2010).

The enzymatic colorimetric techniques outlined by Kostener (1977) were used to measure HDL-c, or high-density lipoprotein cholesterol. Serum total cholesterol was measured spectroscopically using the Allain *et al*., 1974 technique. The Fruchart, 1982 method was used to quantify low-density lipoprotein cholesterol (LDL-c). The Bishop *et al*. (2000) method was used to measure serum total protein. The method outlined by Schirmeister (1964) was used to measure serum creatinine. The ELISA TECO kit was used to measure the level of testosterone hormone in accordance with Richmond's (1973) approach.

2.5. Statistical analysis

A one-way analysis of variance (ANOVA) test was used to conduct statistical analysis on the current data. According to Artimage and Berry (1987), significance was determined using the student "t" test. The mean± standard error (M± SE) was used to express and illustrate the results, and differences were deemed significant when $P < 0.05$, highly significant when $P \leq 0.01$, and very highly significant when $P \leq 0.001$.

3. Results

3.1. Effects *of Amitriptyline, Escitalopram and Clozapine* on RBCs count, Hemoglobin, PCV and Platelets counts

The results of the present study demonstrated that Rats treated with low or high dose of Amitriptyline, exhibited significantly decreased total RBCs count ($p < 0.05$ and $p < 0.01$, respectively) compared to the control group. Similarly, Rats administered low or high dose of Amitriptyline, exhibited significantly decreased ($p < 0.05$ and $p < 0.001$, respectively) Hb content, PCV and PLTs compared to the control group.

Moreover, supplementation with the low or high doses of Clozapine showed significant decrease ($p < 0.01$ and $p < 0.001$, respectively) in total RBCs count, Hb content, PCV and PLTs as compared with the control group. On the other hand, there were non significant alterations ($p > 0.05$) in total RBCs count, Hb content, PCV and PLTs in the groups of rats treated with the low or high doses of Escitalopram as compared to the control group Table (1) and Figure (1).

Table1: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on RBCs, Hemoglobin, PCV and Platelets counts of male albino rats (means ± SE).

Parameter / Group	Erythrocyte ($\times 10^{12}$ / L)	Hemoglobin (g / L)	Pcv (%)	Platelets ($\times 10^{9}$ / L)
G1 control	6.65 ± 0	12.6 ± 0	33.9 ± 0	525 ± 0
Amitriptyline (low) G2	5.2 ± 0.2 *	9.8 ± 0.4 *	30 ± 0.7 *	516 ± 3 *
Amitriptyline (high) G3	3.9 ± 0.3 **	7 ± 0.6 ***	27.2 ± 0.9 ***	513 ± 1 ***
Escitalopram (low) G4	6.8 ± 0.2	12.4 ± 0.3	33 ± 1	532 ± 3
Escitalopram (high) G5	6.9 ± 0.2	12.8 ± 0.5	36 ± 1.3	534 ± 3
Clozapine (low) G6	4.5 ± 0.3 **	9.5 ± 0.9 **	28 ± 0.9 **	518 ± 1.5 **
Clozapine (high) G7	3.2 ± 0.5 ***	6 ± 0.5 ***	24 ± 1 ***	504 ± 1.5 ***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001.

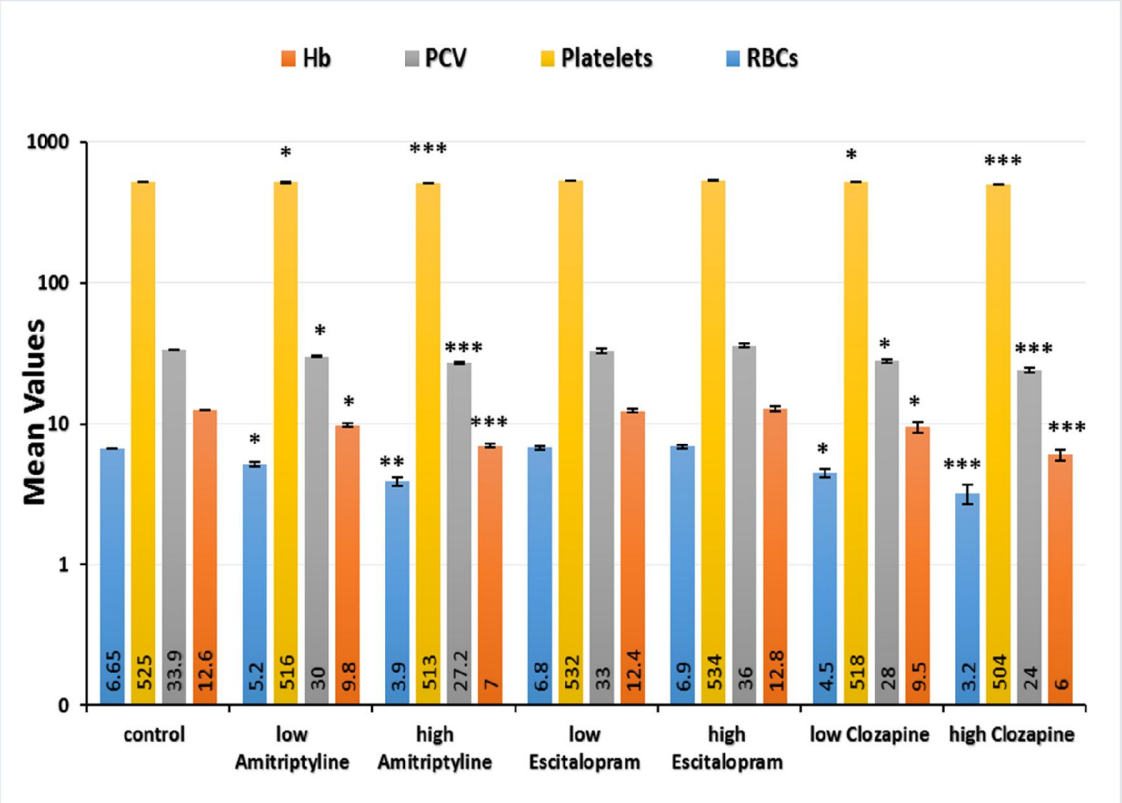

Fig. 1: Effects of administration of the low and high doses of Amitriptyline, Escitalopram and Clozapine on RBCs, Hemoglobin, PCV and Platelets counts of male albino rats.

3.2. Effects *of Amitriptyline, Escitalopram and Clozapine* on Mean corpuscular volume (MCV), Mean corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and Red Cell Distribution Width (RDW).

Hematological parameters like MCV, MCH, MCHC and RDW were estimated in control and treatment groups and are presented in Table (2) and figure (2). Rats administered low or high dose of Amitriptyline, exhibited significantly decreased ($p < 0.05$ and $p < 0.001$, respectively) MCV, MCH,

MCHC and RDW compared to the control group. Also, supplementation with Clozapine at low or high dose showed significant decrease ($p < 0.01$ and $p < 0.001$, respectively) in MCV, MCH, MCHC and RDW as compared to control. On the other hand, administration of the low and high doses of Escitalopram induced a non-significant effect ($p > 0.05$) in MCV, MCH, MCHC and RDW against control group.

Table 2: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on MCV, MCH, MCHC and RDW of male albino rats (means ± SE).

Parameter / Group	MCV (FL)	MCH (Pg)	MCHC (g/dl)	RDW (%)
G1 control	56.5 ± 0	19.5 ± 0	35.4 ± 0	19 ± 0
G2 Amitriptyline (low)	54 ± 0.9 *	16 ± 0.6 *	32 ± 0.6 *	16 ± 0.6 *
G3 Amitriptyline (high)	48.8 ± 0.7***	13± 0.8 ***	29 ± 0.8 ***	12 ± 1 ***
G4 Escitalopram (low)	58 ± 1.1	19.2 ± 2	35.3 ± 1.7	19 ± 1.9
G5 Escitalopram (high)	61.3 ± 2.3	19.4 ± 0.5	37 ± 2.3	19.4 ± 2.3
G6 Clozapine (low)	52 ± 0.7**	17 ± 0.4 **	30 ± 1 **	16.5 ± 0.4 **
G7 Clozapine (high)	45± 1.8 ***	12± 0.7 ***	23 ± 1.7 ***	11.7± 1 ***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001.

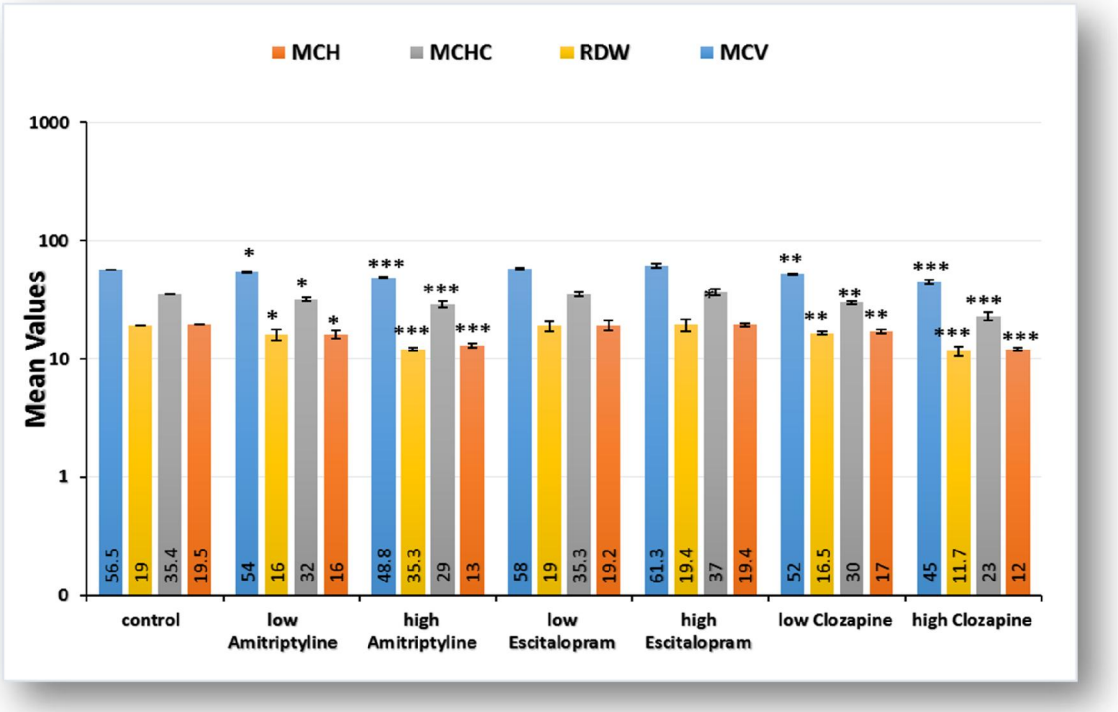

Fig. 2: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on MCV, MCH, MCHC and RDW of male albino rats

3.3. Effects of Amitriptyline, Escitalopram and Clozapine on total leucocytes, neutrophil, monocytes and lymphocytes:

The white blood cells, neutrophil, monocytes and lymphocytes counts of rats after administration of the low or high doses of Amitriptyline, Escitalopram and Clozapine were demonstrated in Table (3) and Figure (3). Rats treated with low dose of Amitriptyline, Escitalopram and Clozapine exhibited non-significant alterations ($p > 0.05$) in White blood cells (WBCs) count, Neutrophils count, Monocytes counts and Lymphocytes count compared to the control group. Moreover, treatment with

high dose of Escitalopram showed non-significant alterations ($p > 0.05$) in White blood cells (WBCs) count, Neutrophils count, Monocytes counts and Lymphocytes count compared to the control group. While, rats that were taken high doses of Amitriptyline and Clozapine showed significantly decreased level ($p < 0.001$) in White blood cells count (WBCs), Neutrophils count, Monocytes counts and Lymphocytes count compared to the control group.

Table 3: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on total leucocytes, lymphocytes, monocytes and neutrophil counts of male albino rats (means ± SE).

Parameter / Group	Leucocyte (×109 / L)	Neutrophil (×109 / L)	Monocyte (×109 / L)	Lymphocyte (×109 / L)
G1 control	2.8 ± 0	22.3 ± 0	6 ± 0	70 ± 0
Amitriptyline (low) G2	2.2 ± 0.4	21 ± 1.9	4.7 ± 1.9	68.7 ± 4.7
Amitriptyline (high) G3	1 ± 0.6 ***	16 ± 0.8 ***	3 ± 0.4 ***	55 ± 2.2 ***
Escitalopram (low) G4	1.8 ± 0.3	21.5 ± 2	5.6 ± 0.8	65.6 ± 5
G5 Escitalopram (high)	2.4 ± 0.4	21 ± 2	5.8 ± 1	66 ± 6
G6 Clozapine (low)	1.7 ± 0.3	18.8 ± 1.8	5.3± 1	67 ± 3
G7 Clozapine (high)	1.4 ± 0.2 ***	14 ± 0.8 ***	2.3 ± 0.4 ***	47 ± 2 ***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001

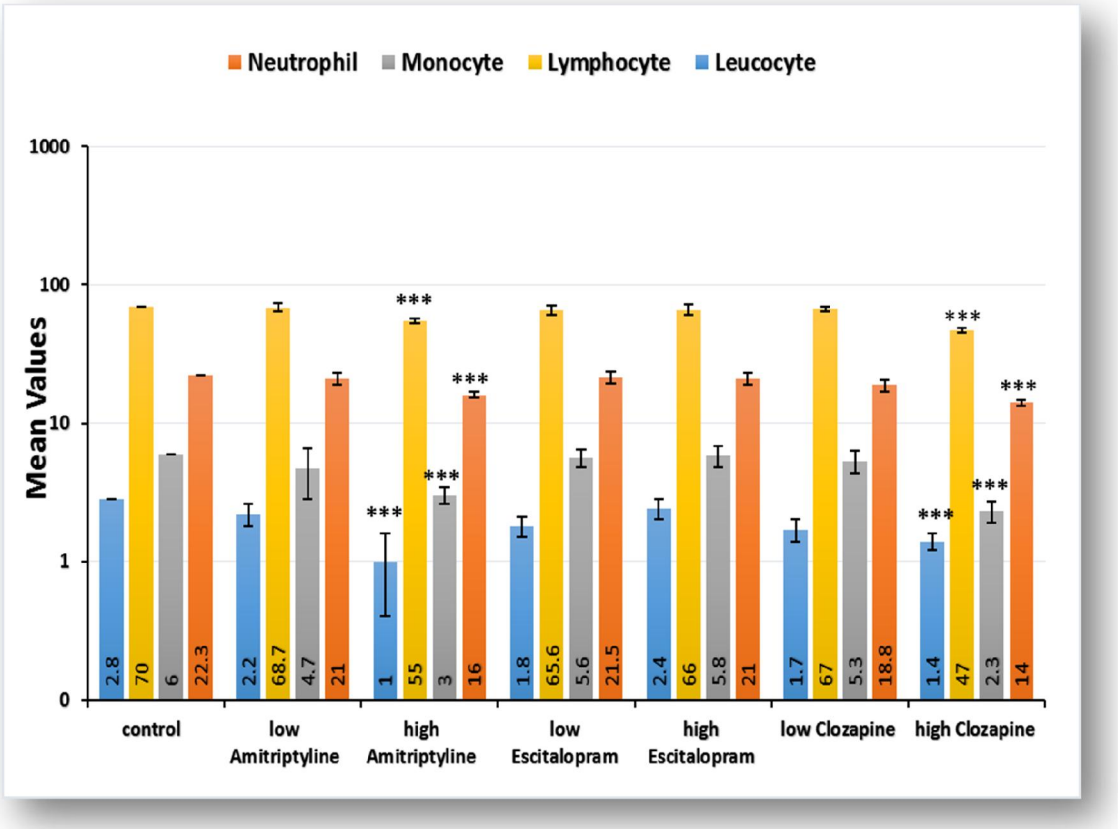

Fig. 3: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on total leucocytes, neutrophil, monocytes and lymphocytes of male albino rats.

3.4. Serum Creatinine, Urea, Uric acid and Testosterone levels

Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on Serum Creatinine, Urea, Uric acid and Total Testosterone level are demonstrated in Table (4) and Figure (4).

Rats administered low or high dose of Amitriptyline and Clozapine exhibited significantly elevated ($p < 0.05$ and $p < 0.001$, respectively) serum creatinine, urea, and uric acid levels compared to the control group. While, administration of the low and high doses of Escitalopram induced a non-significant effect ($p > 0.05$) in serum creatinine, urea, and uric acid levels against control group.

Also, administration of the low and high doses of Escitalopram induced a non-significant effect ($p > 0.05$) in total Testosterone level against control group. While rats treated with low or high dose of Amitriptyline, exhibited significant decrease ($p < 0.05$) level of total Testosterone compared to the control group. Similarly, rats given low or high dose of Clozapine showed significantly decreased ($p < 0.01$ and $p < 0.001$, respectively) level of total Testosterone compared to the control group.

Table 4: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on Creatinine, Blood Urea, Uric Acid and Total Testosterone of male albino rats (means ± SE).

Parameter Group	Creatinine Mg/dL	Blood Urea Mg/dL	Uric Acid Mg/dL	Total Testosterone ng/mL
G1 control	0.47 ± 0	29 ± 0	1 ± 0	1.1 ± 0
G2 Amitriptyline (low)	0.62 ± 0.04 *	43.7 ± 3.9 *	1.7 ± 0.2 *	0.88 ± 0.1 *
G3 Amitriptyline (high)	0.71 ± 0.1 ***	57 ± 3 ***	2.5 ± 0.2 ***	0.5 ± 0.2 *
G4 Escitalopram (low)	0.50 ± 0.05	33.6 ± 2	1.5 ± 0.2	1.5 ± 0.7
G5 Escitalopram (high)	0.53 ± 0.1	33.7 ± 3	1.7 ± 0.2	2.4 ± 0.6
G6 Clozapine (low)	0.65 ± 0.05 *	48.8 ± 4.2 *	1.7 ± 0.2 *	0.8 ± 0.4 **
G7 Clozapine (high)	0.73 ± 0.1 ***	58 ± 2 ***	2.7 ± 0.2 ***	0.3 ± 0.4 ***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001.

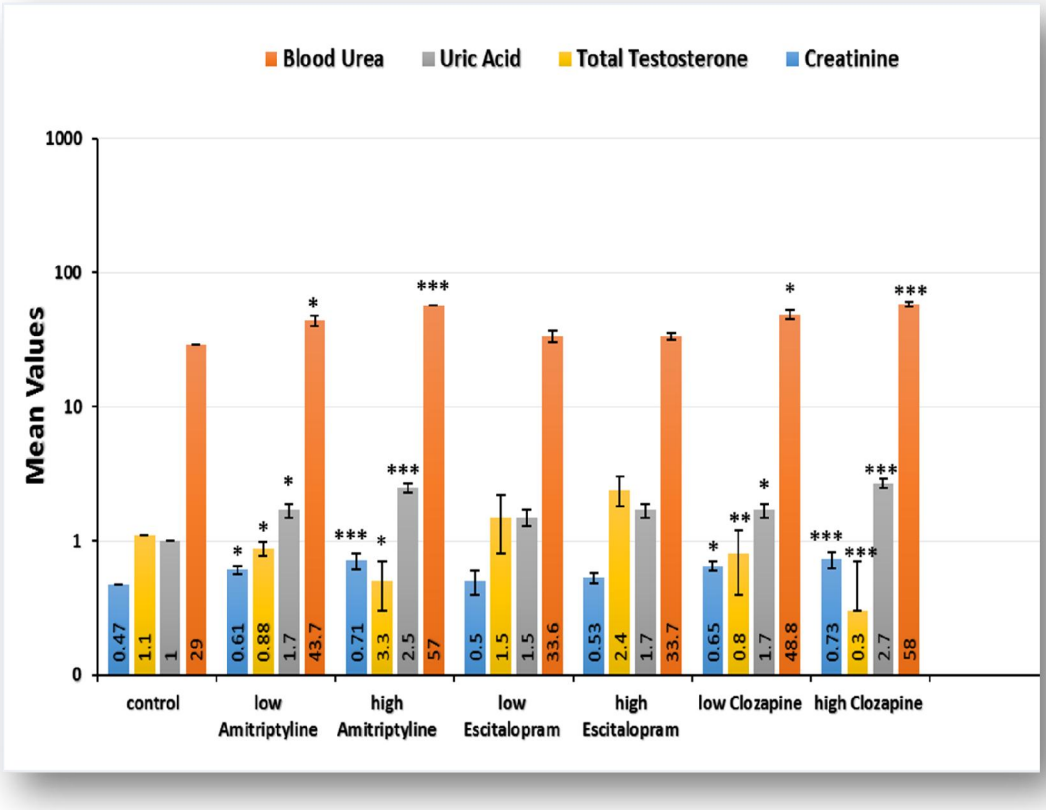

Fig. 4: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on Creatinine, Blood Urea, Uric Acid and Total Testosterone of male albino rats.

3.5. Effects of Amitriptyline, Escitalopram and Clozapine on Total cholesterol (TC), Triglycerides, High-density lipoprotein-cholesterol (HDL-C) level, Low-density lipoprotein-cholesterol (LDL-C) level and very low –Density Lipoprotein (VLDL)

Effects of administration of the low or high dose of Amitriptyline, Escitalopram and Clozapine on serum Total cholesterol (TC), Triglycerides, HDL-C level, LDL-C and VLDL levels are demonstrated in Table (5) and Figure (5&6). Rats administered low or high dose of Amitriptyline or Clozapine, exhibited significantly increased ($p<0.05$ and $p<0.001$, respectively) levels of Cholesterol, Triglycerides, LDL-C and VLDL compared to the control group. However Rats given low or high dose of Amitriptyline or Clozapine, exhibited significantly decreased ($p<0.05$ and $p<0.001$, respectively) HDL-C level compared to the control group. Cholesterol, Triglycerides, LDL-C, HDL-C and VLDL were not significantly influenced ($p > 0.05$) by Escitalopram in both doses in comparison with that of control one.

Table 5: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on total Cholesterol, Triglycerides, HDL, LDL and VLDL levels of male albino rats (means ± SE).

Parameter / Group	Cholesterol mg/dl	Triglycerides mg/dl	HDL Cholesterol mg/dl	LDL cholesterol mg/dl	VLDL Cholesterol mg/dl
(G1)Control	59 ± 0	100 ± 3.8	21 ± 0	6.3 ± 0.3	20 ± 0
Amitriptyline low G2	65 ± 1.9 *	114 ± 3.8 *	16.5 ± 1.2 *	14 ± 1.6 *	26 ± 1.3*
Amitriptyline high G3	71 ± 0.8 ***	134 ± 7 ***	13.6 ± 1 ***	18.4 ± 2 ***	28.4 ± 1***
Escitalopram low G4	62.6 ± 1.3	106 ± 1.8	19.2 ± 0.7	7.4 ± 0.7	22 ± 0.7
Escitalopram high G5	63 ± 1.2	107 ± 2	18 ± 1	11.3 ± 1.6	22.8 ± 1.2
Clozapine low G6	67.2 ± 1.9 *	128 ± 7 *	16 ± 1.8 *	17.4 ± 3.9 *	27.6 ± 1.7*
Clozapine high G7	78 ± 1.3 ***	135 ± 5 ***	14.7 ± 0.8 ***	21 ± 0.7 ***	30 ± 1.3***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001.

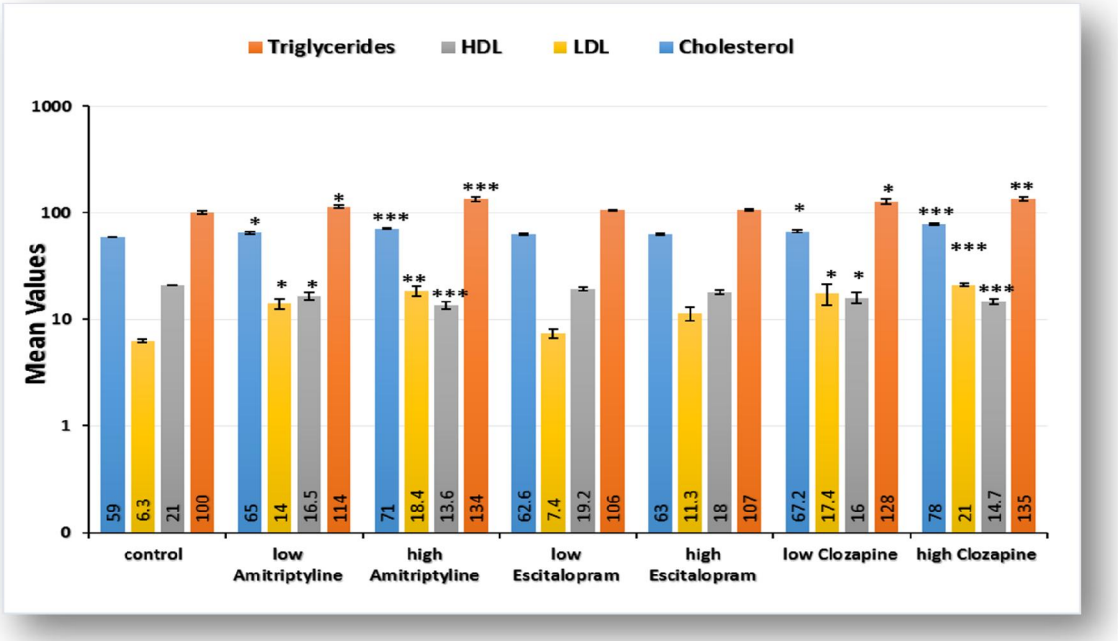

Fig. 5: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on total Cholesterol, Triglycerides, HDL, LDL and VLDL levels of male albino rats.

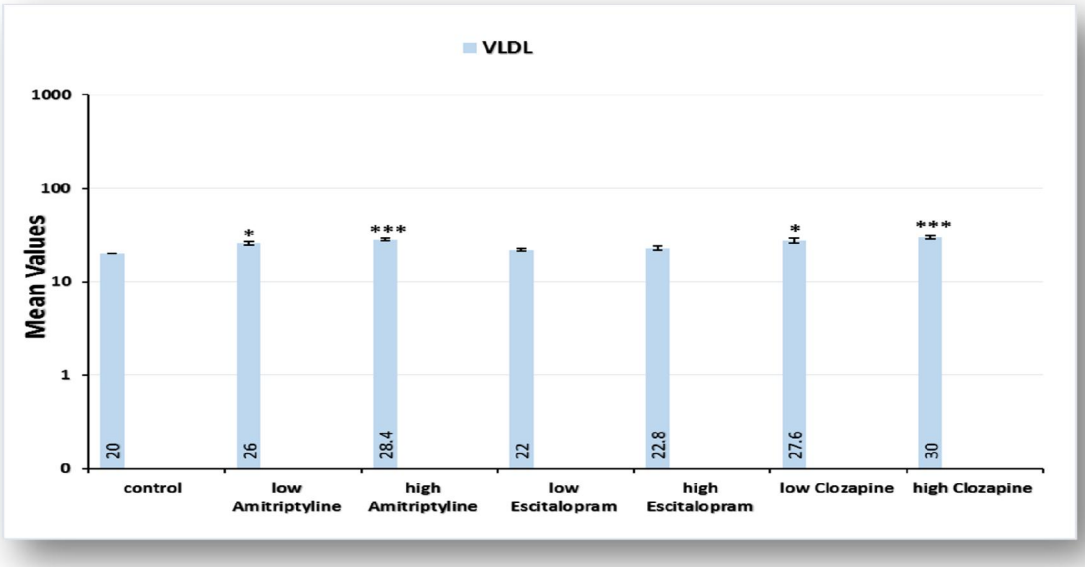

Fig. 6: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on VLDL of male albino rats.

3.6. Total protein, GGT, Albumin, A/G Ratio and No

Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on Total protein, GGT, Albumin A/G Ratio and Nitric oxide (NO) are demonstrated in Table (6) and Figure (7&8).

Administration of the low or high dose of Escitalopram did not induce a significant change ($p > 0.05$) in Total protein, GGT, Albumin, NO and A/G Ratio. Rats given low or high dose of Amitriptyline or Clozapine, exhibited significant decrease ($p<0.05$ and $p<0.001$, respectively) levels of Albumin and A/G Ratio compared to the control group. Moreover, rats given low or high dose of Amitriptyline or Clozapine, exhibited significantly decreased ($p<0.01$ and $p<0.001$, respectively) levels of Total protein and NO compared to the control group. Conversely, rats given low or high dose of Amitriptyline or Clozapine, exhibited significantly increased ($p<0.05$ and $p<0.001$, respectively) levels of GGT compared to the control group.

Table 6: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on GGT, Total Protein, Albumin and A/G Ratio of male albino rats (means ± SE).

Parameter Group	GGT U/l	Total Protein g/dL	Albumin g/dL	A/G Ratio %	NO µM
G1 control	6 ± 0	7.6 ± 0.2	3.4 ± 0.05	1.6 ± 0.1	1.8 ± 0.08
G2 Amitriptyline (low)	8.7 ± 0.8 *	5.4 ± 0.8 **	2.2 ± 0.4 *	0.7 ± 0.2 *	1.1 ±0.1**
G3 Amitriptyline (high)	11.6 ± 0.4 ***	4.2 ± 0.3 ***	1.9 ± 0.04 ***	0.6 ± 0.02 ***	0.8 ±0.1***
G4 Escitalopram (low)	6.4 ± 0.4	8 ± 0.2	3.1 ± 0.2	1.1 ± 0.2	2.4 ±0.4
G5 Escitalopram (high)	7.4 ± 0.5	8.4 ± 0.3	2.8 ± 0.2	1.2 ± 0.1	3.2 ±0.4
G6 Clozapine (low)	10 ± 1 *	5.9 ± 0.3 **	2.4 ± 0.3 *	0.7 ± 0.3 *	0.7 ±0.06**
G7 Clozapine (high)	12 ± 0.2 ***	3.2 ± 0.6 ***	2.2 ± 0.1 ***	0.57 ± 0.1 ***	0.4 ±0.07***

Significant increase or decrease compared with control group * P<0.05 ** P<0.01 ***P<0.001.

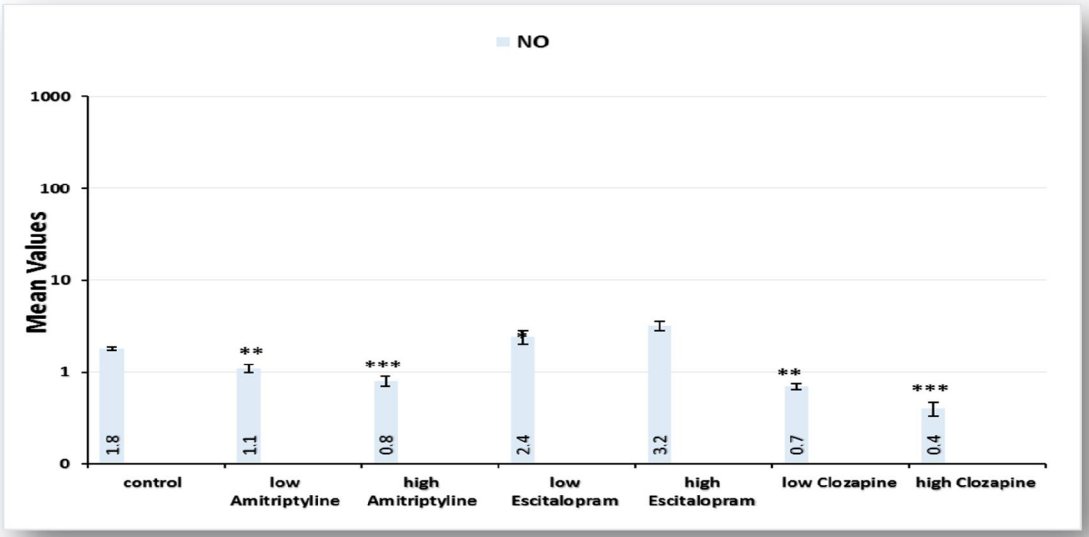

Fig. 7: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on GGT, Total Protein, Albumin and A/G Ratio of male albino rats.

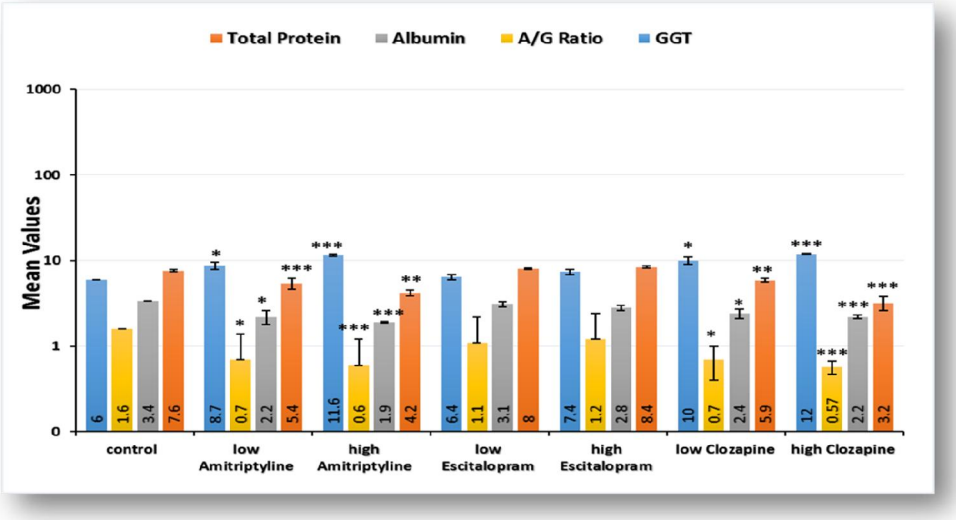

Fig. 8: Effects of low and high doses of Amitriptyline, Escitalopram and Clozapine on NO of male albino rats.

4. Discussion

The present study showed that Amitriptyline and Clozapine treatment in rats can increase urea, uric acid and creatinine levels, indicating kidney toxicity and liver damage, as these levels were significantly higher in the treated groups compared to the control group. Clozapine does not significantly alter creatinine or urea levels in rats, according to some studies, though other studies indicated that clozapine can cause renal damage, reduce antioxidative enzymes, and increase reactive oxygen species in the kidneys of rats. Serum creatinine is the most dependable indicator of renal function, produced at a consistent rate by muscle and nearly entirely filtered by the glomerulus. Additionally, elevated urea levels may indicate renal impairment (Khan *et al*., 2012). The current investigation revealed that rats treated with Amitriptyline displayed elevated levels of urea, uric acid, and creatinine, alongside reduced total protein levels, in comparison to the control group. This may

pertain to the harmful effects of Amitriptyline on renal tissue. The mechanism via which Amitriptyline and clozapine may cause renal injury involves alterations in the glomerulus and tubules, disrupting normal filtration and reabsorption processes, potentially resulting in the presence of red blood cells, proteins, electrolytes, and casts in urine (Aggarwal *et al*., 2019). Concurrently, Reis M and Källén B (2010) suggested that the use of antidepressants may be linked to cystic kidney disease or renal agenesis. A study by Karimi-Khouzani *et al*. (2017) demonstrated that the administration of antidepressants leads to a significant increase in urea levels, while creatinine levels exhibited no significant changes. Conversely, Blumenfield *et al*. (1997) indicated that amitriptyline did not produce significant alterations in renal function markers, including total protein, urea, and creatinine concentrations.

In the present work, administration of Amitriptyline and Clozapine induced significant increase in GGT (gamma-glutamyltransferase), while, Escitalopram showed non significant changes when compared with the control group. Increasing levels of GGT in plasma serve as indication of liver damage, thus, the observed significant increases in these parameters in the present study are pointers to Amitriptyline and Clozapine -induced toxicity in liver tissues. Although some studies in rats showed that amitriptyline did not significantly affect GGT levels, the findings of the present studyare similar to previous studies which demonstrated that Amitriptyline and Clozapine are mostly associated with hepatotoxicity. Cunningham (1965) documented that the administration of Amitriptyline and diazepam resulted in acute hepatic necrosis. The findings align with those of Ebuehi *et al*. (2013), who observed a significant increase in liver enzyme activities in rabbits treated with sertraline, clozapine, and amitriptyline. The findings align with the work of Boles *et al*. (2010), which demonstrated that varying doses of Amitriptyline influence enzymatic levels differently. Clozapine treatment has been shown to increase GGT levels in rats, indicating a potential for clozapine-induced liver damage. In one study, chronic clozapine administration led to an increase in hepatic GGT activity, alongside other signs of hepatotoxicity like increased liver weight, hepatic triglyceride accumulation, and elevated serum AST levels. Also, many cases reported clozapine-induced fulminant liver failure accompanying moderate doses of clozapine (Wu Chou *et al*. 2014).

Findings of the present study showed that administration of Amitriptyline or Clozapine induced significant decrease in total protein and albumin compared with control group. These findings indicate that amitriptyline and Clozapine can negatively impact protein metabolism and organ function, suggesting induction of side effects on liver and kidney functions and structures. Clozapine's effect on total protein and albumin levels in rats is not consistent across all studies; however, one study found that chronic Clozapine treatment significantly decreased total plasma protein and albumin concentrations in rats, while other studies reported no significant difference or focused on different aspects like drug-protein binding or other biochemical changes. The decrease in the level of total protein and albumin in Amitriptyline or Clozapine-treated rats might be due to changes in protein synthesis and/or metabolism (Daabo *et al*., 2022).

The NO is an important pathological mediator that is released during the inflammatory process by the iNOS and its induction is facilitated by the various molecular signaling mechanisms such as NFκB and has been implicated hepatitis (Abraldes *et al*., 2007). The used drugs in the present study inhibited nitric oxide (NO) production which may be related to neuropathic pain-relieving effects. Amitriptyline inhibits nitric oxide (NO) production, particularly inducible nitric oxide synthase (iNOS) expression, in rats, which contributes to its analgesic effect in neuropathic pain models by reducing inflammatory factors and nerve damage. Studies have shown that blocking NO signaling can enhance amitriptyline's efficacy, while elevated NO levels can diminish its beneficial effects on neuropathic pain. Amitriptyline reduces nitric oxide production by downregulating inducible nitric oxide synthase (iNOS) expression. Clozapine has been shown to deplete endothelial NO levels and impair eNOS-mediated vascular relaxation, potentially contributing to cardiovascular effects. However, in microglial cell models (LPS-stimulated cells), clozapine did not significantly affect NO release (Hou *et al*., 2006).

The present study showed significant increase in The levels of total Cholesterol, Triglycerides, LDL-C and significant decrease in HDL-C in the Amitriptyline and Clozapine groups, while, Escitalopram showed non significant changes in the levels of these parameters. Amitriptyline intoxication in rats significantly increased levels of serum cholesterol, triglycerides, and LDL-cholesterol, while HDL-cholesterol levels also showed a significant increase and it was explained that

Amitriptyline affects the heart muscle due to changes in the level of cholesterol and triglycerides (Gurer *et al*., 2006). Also, Kaur *et al.* (2011) showed that Amitriptyline may be responsible for cardiac dysfunction as the concentrations of cholesterol and triglycerides in the serum were significantly elevated in rabbits.

The primary lipid-related metabolic disruption noted after Clozapine intoxication in rats is an increase in triglycerides. Clozapine significantly increases serum triglycerides and can lead to dyslipidemia in rats, with effects on free fatty acids, hepatic lipid accumulation, and altered lipid metabolism gene expression in the liver and adipose tissue. While it has been observed to increase high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels in some studies (Li *et al.,* 2017).

Subsequent studies confirmed liver steatosis and an elevation in plasma triglycerides associated with clozapine treatment (Liu *et al.,* 2017). Furthermore, a single intraperitoneal injection of clozapine has been shown to down-regulate genes associated with lipolysis, resulting in lipid accumulation in the liver of rats (Fernø *et al.,* 2009). Recent studies have focused extensively on hepatic abnormalities related to lipids. Clozapine may exert complex effects on hepatic lipid metabolism, which include (1) the enhancement of de novo lipogenesis; (2) the reduction of lipoprotein internalization and cholesterol clearance; and (3) the diminishment of VLDL secretion through the down-regulation of proteins associated with VLDL secretion, such as apoB and apoE. Collectively, these factors contribute to lipid accumulation in the liver (Chen *et al.,* 2018; Liu *et al.,* 2019; Mahmoud and El-deek 2019; Ren *et al.,* 2019).

The present study showed significant decrease in the levels of testosterone in the Amitriptyline and Clozapine groups, while, Escitalopram showed non significant changes in the levels of this hormone. Sexual problems are common among those with chronic medical conditions, including depression (Derogatis and Burnett, 2008; Lewis *et al*., 2010). According to certain research, excessive dosages of amitriptyline can significantly lower the levels of the hormones testosterone, prolactin, FSH, and LH in experimental rats. It can also slow down testicular growth and interfere with spermatogenic processes. Thus, amitriptyline alters hormone levels and throws off the ratio of testosterone to estrogen, demonstrating the harmful effects of the sex hormone that can cause infertility and sexual dysfunction. The current study's findings are consistent with those of prior research (Williams *et al*., 2010), which showed that medication effects on spermatogenesis and sexual dysfunction seem to be caused by changes in hormone levels, including testosterone.

Some typical and atypical antipsychotics have the potential to negatively affect sexual function (Montejo *et al*., 2021) and have a risk to reproductive health (Park *et al*., 2012). Patients that received second-generation antipsychotics, such as clozapine, experienced reproductive dysfunction. Also, Clozapine treatment in rats is associated with a decrease in plasma testosterone level and affect hormonal status and the process of spermatogenesis in rats (Samadi *et al*., 2019). This effect on testosterone may be linked to impacts on the hypothalamic-pituitary-gonadal (HPG) axis and could be a factor in the testicular degeneration and potential infertility observed in treated animals. in most cases the effects of drugs are reversed after their intake is paused (Semet *et al*., 2017).

The results showed that the low doses of Amitriptyline and clozapine had non significant changes in total WBCs counts, neutrophils, monocytes and lymphocytes counts, but, the high doses of these drugs induced significant decrease in these parameters. The low and high doses of Escitalopram induced non significant changes in these parameters.

Hematological adverse effects are possible with many psychiatric medications. These include anemia, leukocytosis, leukopenia, and neutropenia (Flanagan *et al*., 2008). Neutropenia and thrombocytopenia are common adverse effects associated with nearly all psychiatric drugs (Flanagan *et al*., 2008). Various pathomechanisms, such as peripheral neutrophil destruction, toxic bone marrow suppression, and drug-dependent antineutrophil antibodies, contribute to neutropenia (Stübner *et al.,* 2004).

A thrombocytopenia case occurring after escitalopram use in a 19-year-old female patient with generalized anxiety disorder (Bedel and Korkut, 2021; Flanagan *et al.,* 2008). Yadav et al. described uterine bleeding in a postmenopausal woman after starting escitalopram (Yadav *et al.,* 2018; Stübner *et al.,* 2004).

A study on psychotic patients treated with clozapine. Approximately one-tenth of the patients experienced hematological complications, including thrombocytopenia, anemia, eosinophilia, and

neutropenia (Grover *et al.,* 2020). Two studies indicated neutropenia and agranulocytosis in patients treated with clozapine (Pai and Kelly1996; Mirsal *et al.,* 2002). Among them, eight had fatal agranulocytosis, two had thrombocytopenia, and one was diagnosed with leukemia (Bosch, and Vera, 1998).

Patients with treatment resistant schizophrenia taking clozapine. Side effects, especially hematological ones, were a common reason for discontinuation (Davis *et al.* 2005). Clozapine-related hematological complications, including progressive neutropenia and transient disorders such as eosinophilia and leukocytosis (Hummer *et al.,* 1995; Jagtiani *et al.,* 2020).

The present data demonstrated that administration of Tryptizol, or Clozapine caused a significant decrease in red blood cells, hemoglobin and Platelets. Amitriptyline may cause insignificant decreases in rat red blood cell and platelet counts, though this finding can vary between studies and may be influenced by stress. One study indicated a significant increase in platelet counts associated with amitriptyline treatment in humans, with unknown causes but potential relevance to long-term thromboembolic risk. In rats, amitriptyline has been shown to affect red blood cell parameters, such as reducing microparticle concentrations, increasing red blood cell size, and decreasing osmotic fragility. Another study on male rats found that amitriptyline treatment significantly decreased platelet count and red and white blood cells, while also increasing cardiac enzymes (CK-Mb, CPK, LDH, myoglobin), and lipid profiles, but decreased total proteins. These findings indicate amitriptyline toxicity can lead to adverse hematological changes, including potential acute myocarditis and other cardiotoxic effects (Tousson *et al.,* 2018).

Clozapine can affect red blood cell and hemoglobin levels in rats, potentially causing a type of anemia with decreased hemoglobin and red blood cells, though the effects can be sex-dependent. While some studies suggest the effect is linked to liver damage, others propose it might involve direct bone marrow toxicity or drug-antibody complexes. Platelet levels are also affected by clozapine, with studies showing a significant decrease in platelet count. Also, Clozapine can increase red cell distribution width in rats, though the exact mechanism is still being researched. Studies show conflicting effects on platelets, with some indicating no significant change while others show a reduction in platelet levels in clozapine-treated rats (Atmaca *et al.,* 2013 and Fehsel *et al.,* 2005).

5. Conclusion

The data of this study indicated severe side effects of administration of Clozapine and Amitriptyline to rats daily for a month represented in disturbance in hematological parameters and blood functions, toxicity in kidney and liver functions, in addition to, toxic effects of these drugs concerning sex hormone and have a risk to reproductive health, while, administration of cipralex was more save and without adverse toxicity.

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