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Original Article

Comparative Study of Histological and Histomorphometric Changes between Amitriptyline and Escitalopram in Testis and Epididymis of Male Mice

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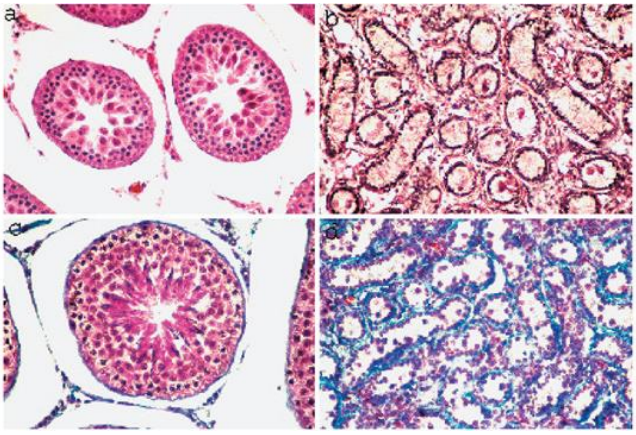
ABSTRACT

The study aimed to discover the effect of Amitriptyline and Escitalopram on body weight and their effects on tissues of the testis and epididymis. These drugs were hypothesized to affect fertility due to their use in the treatment of depression. A group of male mice was administrated amitriptyline and another group Escitalopram for six weeks at dose of (10 mg/kg) twice a day. Then, the tissue sections of the testis and epididymis were prepared, and histopathological revealed histological changes in the testis and epididymis. It was concluded that the use of Amitriptyline and Ascitalopram causes decrease of spermatogonia, proliferation of Sertoli cells, and a decrease in spermatid, which leads to decrease of sperm.

GRAPHICAL ABSTRACT



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Introduction

Male reproductive health is important to public health because the viability and quality of semen are directly or indirectly affected by public health [1]. Antidepressants are medicines used to treat depression, and anxiety-related illnesses [2]. There are many different studies on the negative effect of antidepressants on the male reproductive system [3].

The reason for low male fertility is the use of drugs for long or short periods, as the use of drugs for short-term causes temporary infertility, while the use of drugs for long-term brutally affects fertility [4].

The spermatogenesis process is continuous from puberty and throughout life in humans and takes place in the lumen of the seminiferous tubes, which it the components of the testis, the process of spermatogenesis is a series of events through which sperm develop in the testis [5].

All antidepressants have reported sexual dysfunctions, and clinicians generally mention them as problems maintaining an erection, loss of sexual desire, delayed ejaculation, and decreased sexual arousal [6].

There are several types of antidepressant (SSRIs, NDRIs, MAOIs, SNRIs, TCAs, and atypical antidepressant) and each type has its own mechanism of action and is slightly different from the other types, and therefore takes several ways in its effect on sperm [7].

The data about antidepressants, which leads to a negative effect on the reproductive system are limited and focus mostly on general observations associated with semen parameters and other markers of male fertility [8].

Laboratory studies have shown that antidepressants effect lead to a decrease in the number of sperm cells, changing the morphological appearance, and affecting movement [9].

Because of the lack of available studies on the impact of Amitriptyline and Escitalopram on the histological structure of the testis and epididymis, the current study was conducted to compare the two types.

Materials and Methods

Experimental Animals

The age range of male mice BABL/c used in the experiment was 8-12 weeks with an average weight of 28 gm, the mice were selected from the animal house of the Faculty of Science/Misan university/ Department of Biology. These mice are free of pathogenses, placing them in plastic cages covered with metal mesh and furnished with sawdust, and the mattresses are changed 2 times a week while continuing to clean and sterilize the cages. Animals are handled according to institutional guidelines and approved by the Local Animal Ethics Committee for all experimental procedures. The mice were left for 2 weeks to adapt before the start of the experiment and administration antidepressants at dose (10 mg/kg) twice a day.

The number of animals in this experiment was 90 adult male mice. The male mice were divided into three groups as follows:

Group I (control): This group consisted of 30 male mice that were administered orally normal saline twice a day for six weeks.

Group II: This group consisted of 30 male mice that were administered orally Amitriptyline twice a day at dose (of 10 mg/kg) for six weeks.

Group III: This group consisted of 30 male mice that were administered orally Escitalopram twice a day at a dose (10 mg/kg) for six weeks.

During six weeks, the animals were weighed weekly and clinical signs and behavior were observed.

Every two weeks, ten mice from each group are sacrificed by using chloroform and euthanasia [10]. After the samples are collected testis and epididymis are saved formalin (10%) for 48 hours, and then are dehydrated, cleared, embedding, sections, and stained with hematoxylin, and eosin [11]. At the University of Misan/College of Science/Animal Tissue Laboratory, the tissue samples were examined by light microscope with different magnification powers.

Histomorphometric measurements

Slides of the testis and epididymis were examined. To calculate the diameter of

seminiferous tubules of the testis, diameter of the epididymis duct, and count of (spermatogonia, primary spermatocyte, secondary spermatocyte, and spermatid), an optical microscope was used with (an ocular micrometer) [12].

Statistical Analysis: The mean and standard deviation of the data were analyzed by SPSS Software using one-way ANOVA (Analyses variation) followed by an LSD test for the statistical differences [13].

Results

Clinical study

Body weights

The results showed that there are no significant differences (P>0.05)) in the average weights between the groups during the second and fourth weeks compared with the control group, where the average weight of the control group in the second week was (32.88±3.55), Amitriptyline (29.50±5.54) and Escitalopram (35.40±4.33), while in the fourth week, the average weight of the control group was (34.22±3.36), Amitriptyline (29.00±4.71), and Escitalopram (35.84±4.84).

But in the sixth week, significant differences (P<0.05) were observed in the average weights, where the average weight of the control group was (35.66±2.84), while the weights of the Amitriptyline group decreased and it was (28.26±4.57), as for the weights of the Escitalopram group increased, and the average weight (39.66±2.59), as represented in Table 1.

Table 1: Changes in the bodyweight of male mice over six weeks

Group	Body weights (gram)		
	The 6th week	The 4th week	The 2nd week
Control	32.88 [a] ±3.55	34.22 [a] ± 3.36	35.66 [a] ±2.84
Amitriptyline	29.50 [a] ± 5.54	29.00 [a] ± 4.71	28.26 c ±4.57
Escitalopram	35.40 [a] ± 4.33	35.84 [a] ± 4.84	39.66[b] ± 2.59

**The values represent mean ± SD., vertically different small letters represent a significant difference in (p<0.05) between groups. Similar small letters represent no significant difference.*

Histological study

The testis

Results of the study in the second week showed that the histological structure of the testis consists of seminiferous tubule that it showed regularity of tissue sections of the control group and the presence of all stages of spermatogenesis (spermatogonia, primary spermatocyte, secondary spermatocyte, spermatid, and spermatozoa) as well as the presence of Sertoli cells and Leydig cells, as displayed in Figure 1.

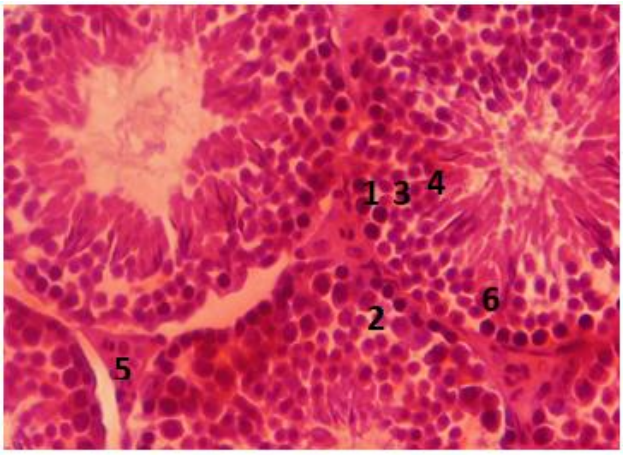

Figure 1: Testis of control male mice two week showing the normal structure (1) spermatogonia, (2) primary sperm, (3) secondary sperm, (4) spermatid, (5) Leydig cells, (6) sertoli cells, (H, Estain, 400x)

While the testis sections for the amitriptyline group showed spaces between spermatogonia cells, decrease inspermatogonia, and clear spaces between the spermatogonia layer and primary spermatocyte layer, as depicted in Figure 2.

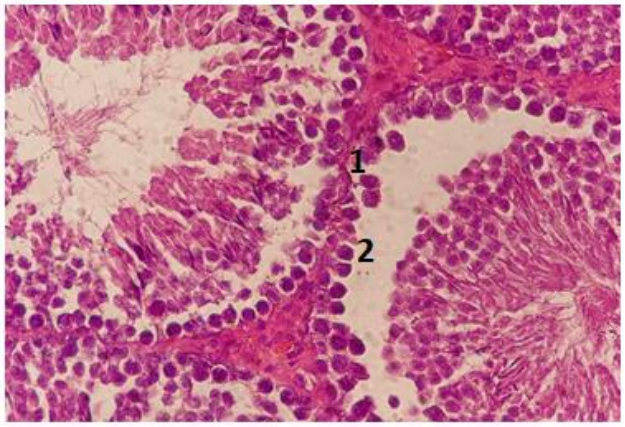

Figure 2: Testis of Amitriptyline male mice two week showing (1) spaces between spermatogonia cells (2) spaces between spermatogonia and primary spermatocyte (H, Estain, and 400 x)

Likewise, the Escitalopram group showed spaces between spermatogonia layer and primary spermatocyte layer, but they are not clear and decrease spermatogoniain mostly in seminiferous tubules, which leads to decrease of spermatogenesis, as demonstrated in Figure 3.

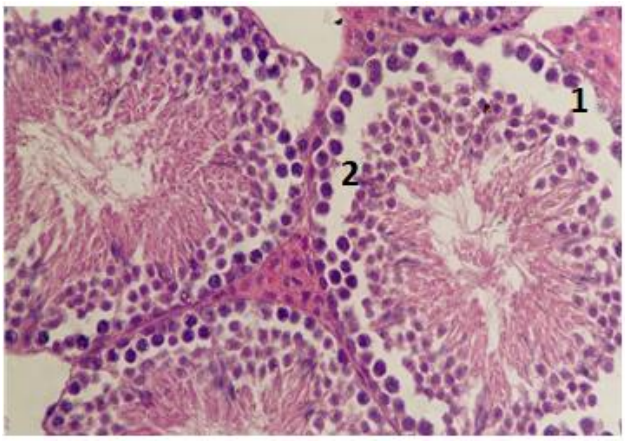

Figure 3: Testis of Escitalopram male mice two week showing (1) decrease spermatogonia, (2) spaces between spermatogonia and primary spermatocyte, (H, Estain, and 400 x).

As for the fourth week, the testis sections for the control group were similar the control group in the second week, as illustrated in Figure 4, while amitriptyline group showed proliferation of Sertoli cells, irregularity of the spermatogonia layer and decrease of its cells, decrease of primary spermatocyte and separation of spermatogonia layer from primary spermatocyte layer, as shown in Figure 5. Furthermore, the Escitalopram group showed irregular layers cells (spermatogonia, primary spermatocyte, and secondary spermatocyte), absence of spermatid layer and lumen wider, as depicted in Figure 6.

While in the sixth week, the control group had no change compared with the second and fourth weeks. Figure 7, as for the Amitriptyline group showed a decrease in spermatid and lumen wider. As it can be seen in Figure 8, the Escitalopram group showed a change in the size of the cells of the primary spermatocyte layer and secondary spermatocyte layer, irregular cell layers (spermatogonia, primary spermatocyte, and secondary spermatocyte), and the absence of spermatid layer and absence lumen (see Figure 9).

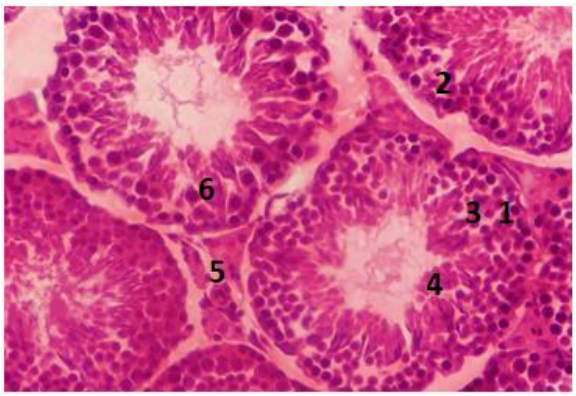

Figure 4: Testis of control male mice four week showing the normal structure (1) spermatogonia, (2) primary sperm, (3) secondary sperm, (4) spermatid, (5) Leydig cells, (6) sertoli cells, (H, Estain, 400x)

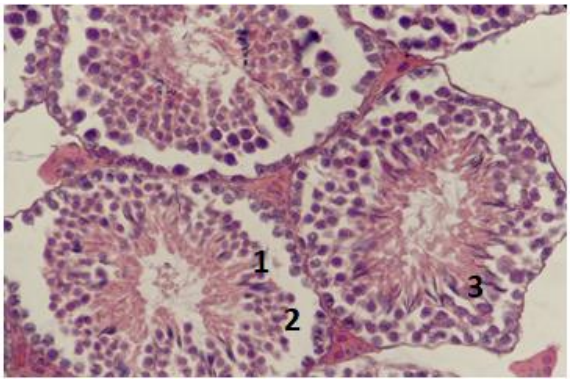

Figure 5: Testis of Amitriptyline male mice four week showing (1) decrease of primary spermatocyte, (2) spaces between spermatogonia layer and primary spermatocyte layer, (3) proliferation sertoli cells, (H, Estain, 400x)

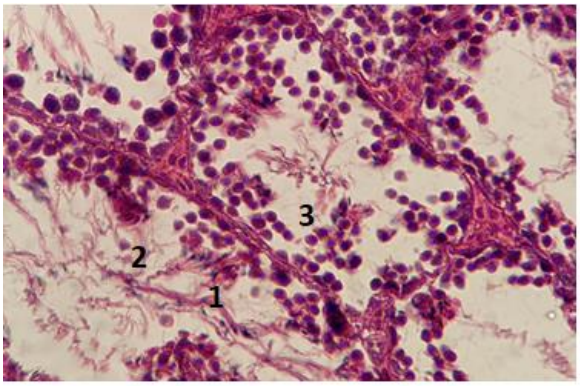

Figure 6: Testis of Escitalopram male mice four week showing (1), absence spermatid layer, (2) lumen wider, (3) irregular layers cells, (H, Estain, 400x)

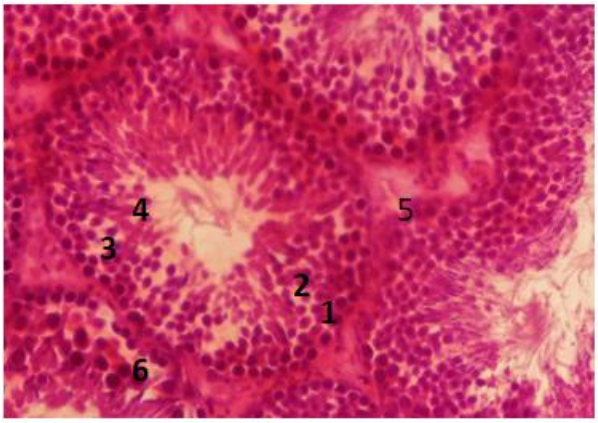

Figure 7: Testis of control male mice six week showing the normal structure (1) spermatogonia, (2) primary sperm, (3) secondary sperm, (4) spermatid, (5) Leydig cells, (6) sertoli cells, (H, Estain, 400x).

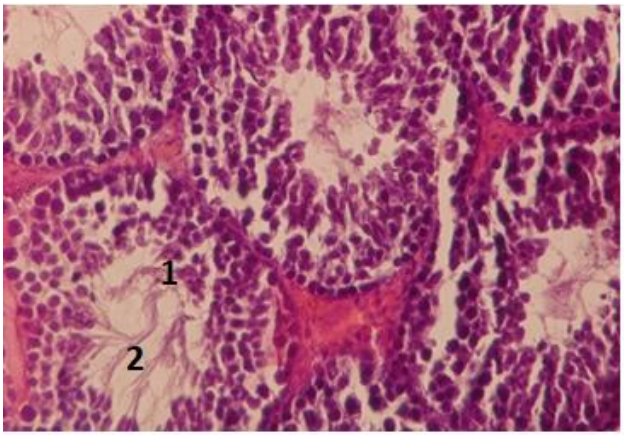

Figure 8: Testis of Amitriptyline male mice six week showing (1) decrease spermatid, (2) lumen wider, (H, Estain, 400x)

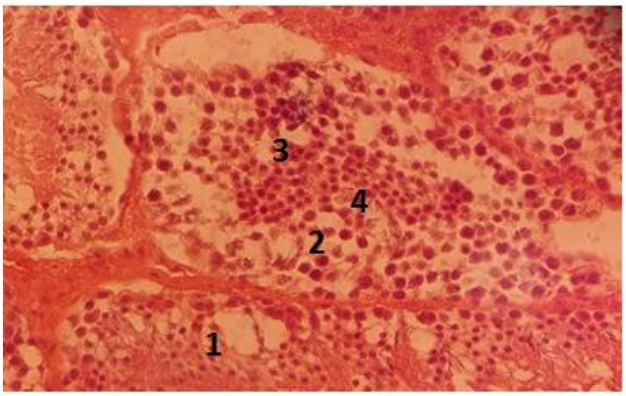

Figure 9: Testis of Escitalopram male mice six week showing (1) change the size of the cells (2) irregular cell layers (3) absence spermatid layer (4) absence lumen, (H, Estain, 400x)

The epididymis

The result of the study in the second week showed that the histological structure of Epididymis in the control group is lined with pseudo-stratified columnar epithelium, this epithelium stereociliated and lumen filled with mature sperms, as displayed in Figure 10, while the epididymis section for the Amitriptyline group showed normal tissue of the epididymal duct and the presence of many sperms in the lumen of the epididymis, as illustrated in Figure 11. In addition, Escitalopram group showed hypertrophy of epithelial cells and the lumen contains small numbers of sperm, as shown in Figure 12.

As for the fourth week, the epididymis sections for the control group similar to the control group in the second week, as depicted in Figure 13, while the Amitriptyline group showed a normal epithelium layer, lumen filled with mature sperms and the presence of a gap between the cells of the epithelium, as indicated in Figure 14, and Escitalopram group, it showed hypertrophy of epithelial cells, the presence of rounded immature sperms, and a decrease of sperm, as depicted in Figure 15.

While in the sixth week, the control group no change compared with the second and fourth weeks, as demonstrated in Figure 16. As for the Amitriptyline group showed hypertrophy of epithelial cells, absence of sperms in the lumen, and the lumen appears narrow and irregular, as displayed in Figure 17, and the Escitalopram group, it showed the epithelial cell layer changed from pseudo-stratified columnar type to the simple type, and the cell shape changed from the columnar to the cuboidal shape and lumen contained mature sperms, as illustrated in Figure 18.

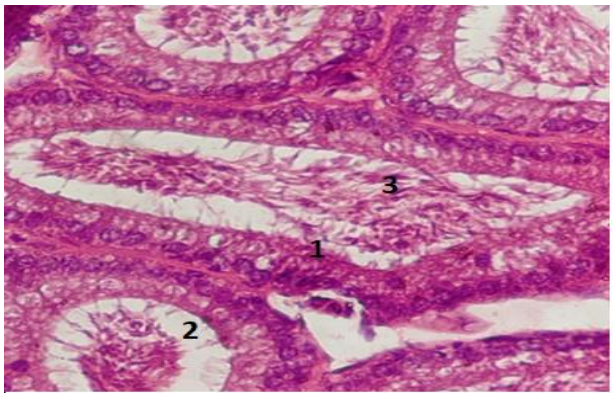

Figure10: Epididymis of control male mice two week showing (1) normal pseudostratified columnar epithelium, (2) lumen filled with mature sperms (3) mature sperms, (H, Estain, 400x)

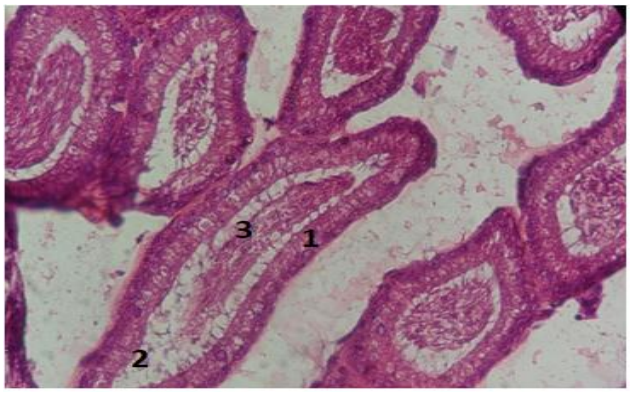

Figure 11: Epididymis of Amitriptyline male mice two week showing (1) normal pseudostratified columnar epithelium, (2) lumen filled with mature sperms, (3) mature sperms, (H, Estain, 400x)

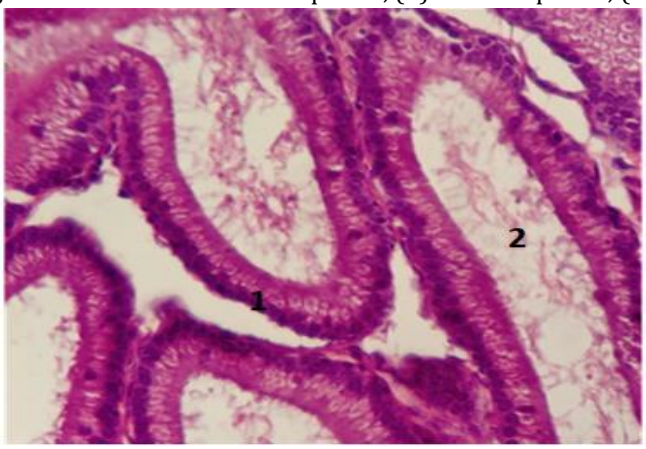

Figure 12: Epididymis of Escitalopram male mice two week showing (1) hypertrophy of epithelial cells, (2) decrease of sperms, (H, E stain, 400 X)

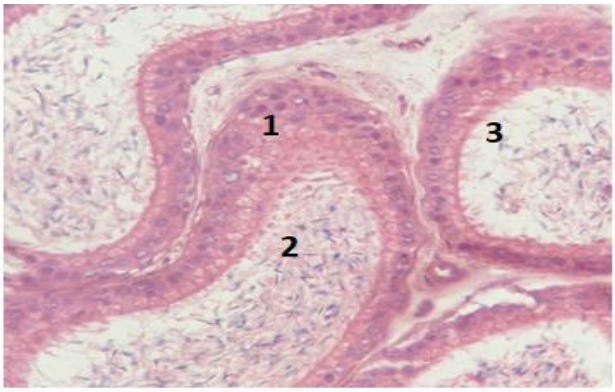

Figure 13: Epididymis of control male mice four week showing (1) normal pseudostratified columnar epithelium, (2) lumen filled with mature sperms, (3) mature sperms, (H, E stain, 400 X)

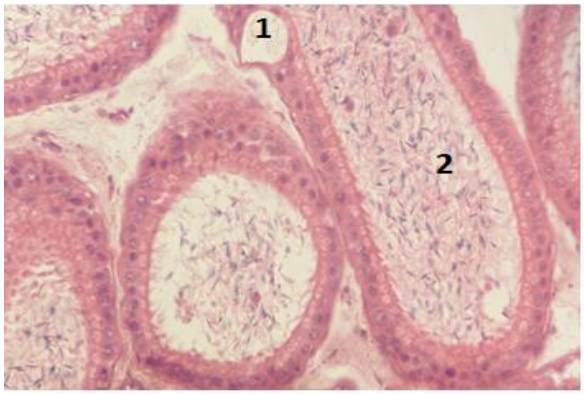

Figure 14: Epididymis of Amitriptyline male mice four week showing (1) gap between the cells of the epithelium, (2) lumen filled with mature sperms, (H, E stain, 400 X)

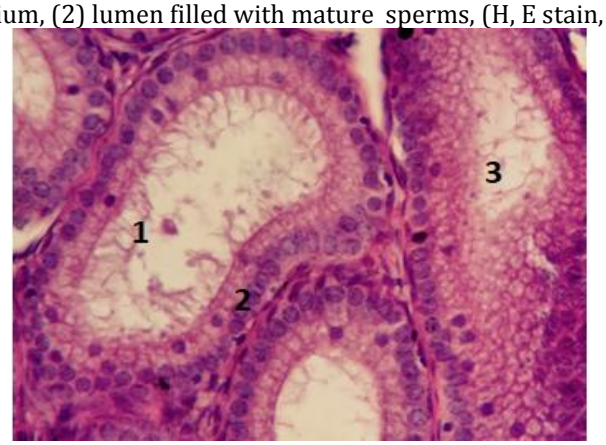

Figure 15: Epididymis of Escitalopram male mice four week showing (1) presence of rounded immature sperms, (2) hypertrophy of epithelial cells, (3) decrease of sperm (H,E stain, 400 X)

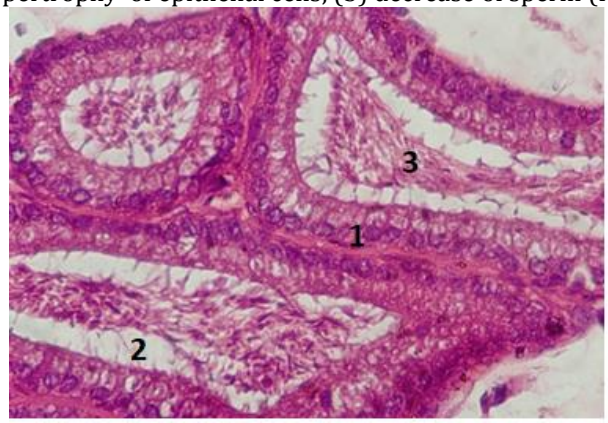

Figure 16: Epididymis of control male mice six week showing (1) normal pseudostratified columnar epithelium, (2) lumen filled with (3) mature sperms, (H, E stain, 400 X).

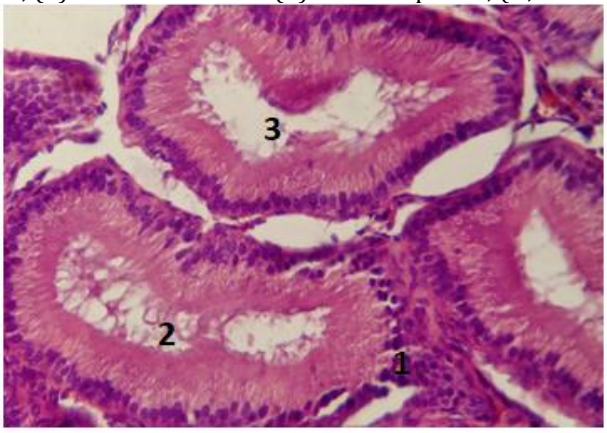

Figure 17: Epididymis of Amitriptyline male mice six week showing (1) hypertrophy of epithelial cells, (2) lumen appears narrow and irregular, (3) absence of sperms in lumen, (H, E stain, 400 X)

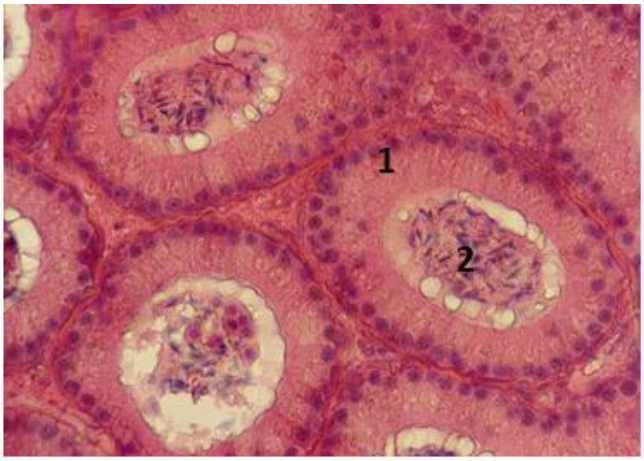

Figure 18: Epididymis of Escitalopram male mice six week showing (1) simple layer, (2) lumen contained mature sperms, (H, E stain, 400 X)

Histomorphpmtric study

Diameter of seminiferous tubules

The results of the study showed that there are no significant differences (p>.0.05) in the diameter of seminiferous tubules in both groups Amitriptyline and Escitalopram compared with the control group over six weeks. In the second week, the diameter of the control group was (1.73±0.11), Amitriptyline (1.75±0.14), and Escitalopram (1.77±0.21), while in the fourth week, the diameter of the control group was (1.73±0.11), Amitriptyline (1.75±0.26), and Escitalopram (1.73±0.08), as for in the sixth week, the diameter of the control group was (1.73±0.11), Amitriptyline (1.74±0.20), and Escitalopram (1.68±0.24), as listed in Table 2.

Diameter of Epididymis duct

The results of the study showed that there are no significant differences (p>.0.05) in the diameter of the epididymis duct in both Amitriptyline and Escitalopram groups compared with the control group over six weeks. In the second week, the diameter of the control group was (1.33±0.29), Amitriptyline (1.29±0.09), and Escitalopram (1.25±0.08), while in the fourth week, the diameter of the control group was (1.33±0.29), Amitriptyline (1.28±0.05), and Escitalopram (1.25±0.15), as for in the sixth week, the diameter of the control group was (1.33±0.29), Amitriptyline (1.25±0.15), and Escitalopram (1.26±0.09), as depicted in Table 2.

Table 2: Changes in diameter of seminiferous tubules and epididymis duct of male mice over the six weeks

Diameter of seminiferous tubule (µm)				Diameter of Epididymis duct (µm)		
Group	The 2nd week	The 4th week	The 6th week	The 2nd week	The 4th week	The 6th week
Control	1.73 a ± 0.11	1.73 a ± 0.11	1.73 a ± 0.11	1.33 a ±0.29	1.33 a ±0.29	1.33a ±0.29
Amtriptyline	1.75 a ± 0.14	1.75 a ± 0.26	1.74 a ± 0.20	1.29a ± 0.09	1.28 a ±0.05	1.25a ±0.15
Escitalopram	1.77 a ± 0.21	1.73 a ± 0.08	1.68 a ± 0.24	1.25 a ± 0.08	1.25 a ± 0.15	1.26 a ±0.09

**The values represent mean ± SD. *Different small letters represent significant differences in (p< 0.05) between groups. *Similar small letters represent no significant difference.*

Count of spermatogonia

The result of the study showed that there were no significant differences (p>0.05) in the count of spermatogonia cells in each Amitriptyline and Escitalopram group during the second week compared with the control group, where the count of the control group was (61.2±6.53), Amitriptyline (64.6±3.78), and Escitalopram (54.8±5.93).

While in the fourth week period, the count of spermatogonia cells showed a significant

decrease ($p<0.05$) in the Amitriptyline and Escitalopram group, and the decrease in the Amitriptyline group was less than the decrease in the Escitalopram group compared with the control group, where the count of the control group was (59.2±5.93), Amitriptyline (26.8±2.28), and Escitalopram (24.2±1.64).

Moreover, in the sixth week, no significant differences($p>0.05$) were observed in the count of spermatogonia cells in each of the Amitriptyline and Escitalopram group compared with the control group, where the count of the control group was (58.4±5.36), Amitriptyline (61.0±2.91), and Escitalopram (57.8±3.11), as listed in Table 3.

Count of primary spermatocytes

The result of the study showed that there was a significant decrease ($p<0.05$) in the count of primary spermatocyte cells in each of the Amitriptyline and Escitalopram group during the second week, and the decrease in the Escitalopram group was less than decrease in the Amitriptyline group compared with the control group, where the count of the control group was (57.40±8.84), Amitriptyline (37.2±4.81), and Escitalopram (40.6±3.84).

While during the fourth week, the number of primary spermatocyte cells showed a significant decrease ($p<0.05$) in the Amitriptyline and Escitalopram group, and the decrease in the Amitriptyline group was less than the decrease in the Escitalopram group compared with the control group, where the count of the control group was (55.6±10.04), Amitriptyline (28.2±3.11), and Escitalopram (22.0±4.30).

In addition, As for as the sixth week, no significant differences ($p>0.05$) were observed in the count of primary spermatocyte cells in each of the Amitriptyline and Escitalopram group compared with the control group, where the count of the control group was (57.2±9.68), Amitriptyline (48.4±10.28), and Escitalopram (49.2±10.54), as presented in Table 3.

Count of secondary spermatocytes

The result of the study showed that there was a significant decrease ($p<0.05$) in the count of the secondary spermatocyte cells in each Amitriptyline and Escitalopram group during the second and fourth weeks, and decrease in the Escitalopram group was less than decrease in the Amitriptyline group compared with the control group, in the second week, the count of the control group was (59.0±7.87), Amitriptyline (24.6±5.03), and Escitalopram (31.4±2.88), while in the fourth week, the count of the control group was (59.4±5.89), Amitriptyline (29.2±7.36), and Escitalopram (30.4±5.68).

In the sixth week, no significant differences ($p>0.05$) were observed in the count of the secondary spermatocyte cells for the Amitriptyline group, while the Escitalopram group showed that there was a significant decrease ($p<0.05$) compared with the control group, where the count of the control group was (56.6±7.73), Amitriptyline (51.0±1.58), and Escitalopram (49.8±1.92), as indicated in Table 3.

Count of spermatids

The result of the study showed that there was a significant decrease ($p<0.05$) in the count of spermatid cells in each of the Amitriptyline and Escitalopram group during the second and the fourth weeks, and the decrease in the Escitalopram group was less than the decrease in the Amitriptyline group compared with the control group, in the second week, the count of the control group was (55.4±5.55), Amitriptyline (26.0±3.74), and Escitalopram (29.4±6.02), while in the fourth week, the count of the control group was (56.2±6.61), Amitriptyline (23.0±2.00), and Escitalopram (24.4±3.05).

In the sixth week, no significant differences($p>0.05$) were observed in the count of spermatid cells for Amitriptyline and Escitalopram group compared with the control group, where the count of the control group was (56.2±6.05), Amitriptyline (57.0±9.05), and Escitalopram (54.6±4.33), as indicated in Table 3.

Table 3: Changes in the count of (spermatogonia, primary spermatocyte, secondary spermatocyte, and spermatid) in male mice over the six weeks

Count of					
Group	Week	Spermatogonia	Primary Spermatocyte	Secondary Spermatocyte	Spermatid
Control	The 2nd week	61.2a ±6.53	57.40 a ±8.84	59.0 a ±7.87	55.4 a ±5.55
	The 4th week	59.2 a ±5.93	55.6 a ±10.04	59.4 a ±5.89	56.2 a ±6.61
	The 6th week	58.4a ±5.36	57.2a ±9.68	56.6a ±7.73	56.2a ±6.05
Amtriptyline	The 2nd week	64.6a ± 3.78	37.2c ± 4.81	24.6c ± 5.03	26.0c ± 3.74
	The 4th week	26.8 b ±2.28	28.2 b ±3.11	29.6c ± 5.03	23.0 c ±2.00
	The 6th week	61.0a ±2.91	48.4a ±10.28	51.0a ±1.58	57.0a ±9.05
Escitalopram	The 2nd week	54.8 a ± 5.93	40.6 b ± 3.84	31.4 b ± 2.88	29.4 b ± 6.02
	The 4th week	24.2 c ± 1.64	22.0 c ± 4.30	30.4 b ± 5.68	24.4 b ± 3.05
	The 6th week	57.8 a ±3.11	49.2 a ±10.54	49.8 b ±1.92	54.6 a ±4.33

**The values represent mean ± SD. *Different small letters represent a significant difference in (p< 0.05) between groups. *Similar small letters represent no significant difference.*

Discussion

The study showed that Amitriptyline causes weight decrease and Escitalopram increase weight in the sixth week of the experiment.

The explanation for the weight change due to the hormonal disturbance, this study is consistent with [14] which explained the hypothalamus sends signals to the anterior pituitary gland, and there is direct control of metabolic functions and the secretion of hormones that regulate other glands.

Another study [15] indicated that Amitriptyline reduces Ghrelin and Cortisol. Ghrelin lead to food intake [16], and high levels of cortisol are associated with weight increase, especially abdominal obesity [17].

The results of our study are compatible with [18], where this study showed that the use of antidepressant drugs causes an increase in weight and cannot be controlled in weight even after regular diet and exercise.

Another study showed that antidepressants cause an increase in body weight by influencing the level of leptin [19]. Which is a hormone secreted by fat cells and works to regulate food intake, metabolism, energy balance, and neuroendocrine and immune functions [20].

The current study showed that the Amitriptyline and Escitalopram through the histological diagnosis over six weeks of taking the two treatments lead to decrease in spermatogonia and clear spaces between the spermatogonia layer and primary spermatocyte layer, proliferation of Sertoli cells, and a decrease in spermatid and lumen wider in testis. Histological epididymis image showed the epithelial cell layer changed from the pseudostratified columnar type to the simple type, and the cell shape changed from the columnar to the cuboidal shape. The explanation for these changes may be due to an imbalance in hormone levels.

These results are in agreement with the study that showed Amitriptyline leads to a decrease in the testicular function [21]. Another study showed that Amitriptyline causes a decrease in testosterone and a decrease in sperm count which was evident from the morphological changes in the testicular tissue. [22].

Some studies showed that impotence and decreased spermatogenesis are due to changes in (FSH, LH, and Testosterone) [23].

Antidepressant cause distorted of the seminiferous tubules. [24], and this result is also consistent with the findings of the current study.

Furthermore, another explanation for the result is that antidepressant cause the induction of lipid peroxidation and this causes the release of free radicals, which leads to membrane disorganization, causing membrane fluidity [25,34].

Cell damage in the reproductive organs may be a result of oxidative stress and the production of reactive oxygen species, SSRIs stimulate DNA fragmentation and ROS formation [26,33].

The imbalance between the production of reactive oxygen species and defensive antioxidants stimulates oxidative stress, which causes damage to DNA, proteins, and lipids, which causes apoptosis and necrosis. [27].

When spermatozoa move from the testis to the epididymis, they are nonfunctional gametes. As it passes through the epididymis, it matures and acquires progressive movement and can fertilize the ova, the reason for the maturation of spermatozoa when the moves to the epididymis are the interaction of spermatozoa with proteins that are made and secreted in the epididymis epithelium. About 40% of infertility men have an unknown cause that may be the result of disorders of spermatozoa maturation and this confirms understanding of the function of the epididymis [28].

LH receptors are located in the epididymis, LH is important for the normal function and morphology of the epididymis [29, 32].

The hypothalamic-pituitary-adrenal (HPA) axis is involved in anxiety disorders, mood disorders, insomnia, and posttraumatic stress disorders, and thus antidepressant regulate axis function (HPA). When serotonin is elevated in the hypothalamus by antidepressants, it causes activation of the (HPA) axis. The paraventricular nucleus of the hypothalamus secretes corticotropin-releasing hormone (CRH) which has a role in regulating the anterior pituitary gland and vasopressin which stimulates the secretion of adrenocorticotropic hormone (ACTH), which is the production cycle of glucocorticoids acts on the hypothalamus and pituitary to suppress the production of (CRH and ACTH) by negative feedback, which causes a lack of secretion (FSH, LH) and is necessary for spermatogenesis. Increases the level of serotonin suppresses the hypothalamic-pituitary-adrenocortical axis and leads to a lack of (FSH, LH, and T) testosterone acts directly on the germinal epithelium [30, 31].

Conclusion

The result of our study showed that administration of Amitriptyline and Escitalopram to male mice negatively affects weight, testicular, and epididymis tissues, and thus caused damage to spermatogenesis.

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Conflict of Interest

The authors there are no differences in the interests.

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