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Cardiac and hepatic side effects of fluoxetine in male and female adolescent rats

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Abstract

Background: Fluoxetine (FLX) is widely prescribed as an antidepressant medicine in the juvenile population.

Objectives: Although some adverse effects of FLX have been reported in adults, the present study aimed to investigate the side effects of FLX treatment during adolescence on the cardiac and hepatic systems.

Methods: Male and female rats were gavaged with FLX (5 mg/kg/day) on postnatal days (PND) 21 to PND 60. Following treatment, blood samples were collected and hepatic enzymes were evaluated. The specimens of the liver and heart of animals were subjected to histopathological assessment.

Results: Fluoxetine significantly raised serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in males, whereas the aspartate aminotransferase (AST) level increased in both male and female animals. In the histopathological study, hepatic plates were more seriously affected, and the sinusoids were irregular in adolescent male rats. Degenerative changes were observed especially in the first and second hepatic zones of FLX-treated male rats. Signs of inflammation and accumulation of lymphoid groups were frequently observed in the portal triad of the hepatic lobules. These alterations were more severe in male livers. Minimum or nearly normal changes were observed in female liver slides. In addition, the histological assessment indicated that treatment with FLX during adolescence also increased the heart's weight and the wall thickness of the right and left ventricles (hypertrophy) in male and especially female animals.

Conclusion: Our findings may provide new insights into the cardiac and hepatic adverse effects of FLX.

KEYWORDS
adolescence, cardiac side effects, fluoxetine, hepatic side effects

1 | INTRODUCTION

Psychiatric disorders such as depression and obsessive-compulsive disorder in young people are generally treated with antidepressant drugs. One of the most important and widely used drugs is fluoxetine (FLX), a selective serotonin reuptake inhibitor (SSRI) that is administrated to treat behavioral symptoms in young adolescents and children.[1–5] Even though the treatment efficacy of FLX has been demonstrated in children, the adverse effects of this drug are reported in adolescents.[6–8] FLX also is a fluorine-containing drug. It has been shown that chronic fluoride exposure (F-) induces excessive production of free radicals, affects the antioxidant defense system, and induces

List of abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAT, catalase; FLX, fluoxetine; H and E, hematoxylin and eosin; PND, postnatal day; SSRI, selective serotonin reuptake inhibitor; TG, triglyceride.

liver damage.[9,10] Furthermore, chronic fluoxetine administration results in lipid accumulation and the development of nonalcoholic fatty liver disease through the up-regulation of tryptophan hydroxylase mRNA expression and intracellular serotonin content.[11] Feng et al.[12] have shown that FLX induces hepatic lipid accumulation by promoting lipogenesis and reduction of lipolysis in the primary mouse hepatocytes. FLX also inhibits carboxylesterases, which in turn aggravates lipid accumulation. This study supports the notion that FLX exposure induces metabolic adverse effects through direct disorders of lipid homeostasis in the liver, perhaps in the adipose tissue.

The cardiac side effects and toxicity of antidepressants including intraventricular conduction slowing, atrial fibrillation or bradycardia, and syncope have been documented in the literature. FLX inhibits Na+ and Ca2+ channels and leads to cardiac electrophysiological effects.[13] The inhibition of these channels by FLX may explain the cardiac adverse effects that occur occasionally with this drug.[14] Case reports indicated that treatment with FLX leads to moderate pulmonary hypertension, mild mitral and tricuspid regurgitation, and concentric left ventricular hypertrophy in women. Another study demonstrated that normal cardiac valves became normal 10 months after discontinuing FLX and there was no evidence of pulmonary hypertension.[15] It has been shown that the treatment of pregnant rats with FLX at the gestational age of 11–21 days could induce pulmonary hypertension in the fetal rat due to the dysregulated proliferation of vascular smooth muscle of pulmonary vessels.[16] Therefore, the present study was designed to evaluate the effects of FLX administration (40 days) during adolescence on the cardiac and hepatic systems.

2 | MATERIALS AND METHODS

2.1 | Animals

All experiments applying the animals were carried out according to the Ethics Committee of the Ardabil University of Medical Sciences in accordance with the "National Institutes of Health NIH Guide for the Care and Use of Laboratory Animals" (Ethics Code: IR.ARUMS.AEC.1401.034). Male and female Wistar rats were obtained from Pasteur's Institute (Tehran, Iran) and kept in the animal house at the School of Medical Sciences. The animals were housed in a 12-h light–dark cycle. The temperature was 23 ± 1°C, and the humidity was 54%. Animals had free access to water and were fed with a pellet rodent diet ad libitum. The male and female rats were maintained in the big cage for mating. The pregnant female rat was kept individually in the standard cage after a successful mating. After delivery on postnatal days (PND) 1, litters were culled into 10 pups (five per sex when possible). In PND21, they were weaned from their mothers. After that, female pups were housed with each other in a big cage for the induction of a similar estrus cycle. According to the techniques adopted in our previous experiments, most of the females had similar estrus cycles.[17,18]

2.2 | Experimental rats and drug treatment

A total of 32 male and female pups ($n = 8$) were randomly distributed into four groups. Two groups included male and female FLX-treated pups in which the rats were gavaged with FLX (5 mg/kg/day) on PNDs 21–60. The other two groups of male and female rats were assigned to the control groups in which the animals received distilled water. FLX was dissolved in distilled water and prepared freshly. FLX dose selection was chosen according to the previously published method and oral drug administration.[19] A dose of 5 mg/kg FLX is commonly used in rat experiments and is sufficient to block serotonin reuptake.[20,21] After completion of the experiment, the animals were killed under deep anesthesia using atmospheric carbon dioxide (CO2) in the desiccator.

2.3 | Serum hepatospecific enzyme markers

Blood samples were taken directly from the heart via cardiac puncture. Serum was collected by centrifugation at 1500*g* for 10 min at 4°C. Serum ALT, AST, and ALP activity was measured by the Reitman–Frankel method in all experimental groups. Enzyme activity was reported as International Units per liter (IU/L).

2.4 | Histopathological investigation of the hepatic tissues

After the completion of the experiment, some fragments of the liver were collected and fixed in a 10% formalin solution. Paraffin-embedded samples were then sectioned at 5 μm thickness and stained with hematoxylin and eosin (H&E).[22]

2.5 | Cardiac structure assessment

Twenty-four hours after the end of FLX treatment, hearts were removed and weighed. After trimming of pericardium, fat, and blood vessels, the post-mortem wall thickness of the right and left ventricles was measured using manual calipers.

2.6 | Statistical analysis

Data from ALP, AST, and ALT were analyzed using the two-way ANOVA, with treatment and sex as factors. Tukey's post hoc test was used for multiple comparisons among groups. The results of the weight of the heart and thickness of the ventricles were analyzed using an independent *t* test. The data are expressed as mean ± standard error of the mean (S.E.M.). Statistical significance was set at $p < 0.05$.

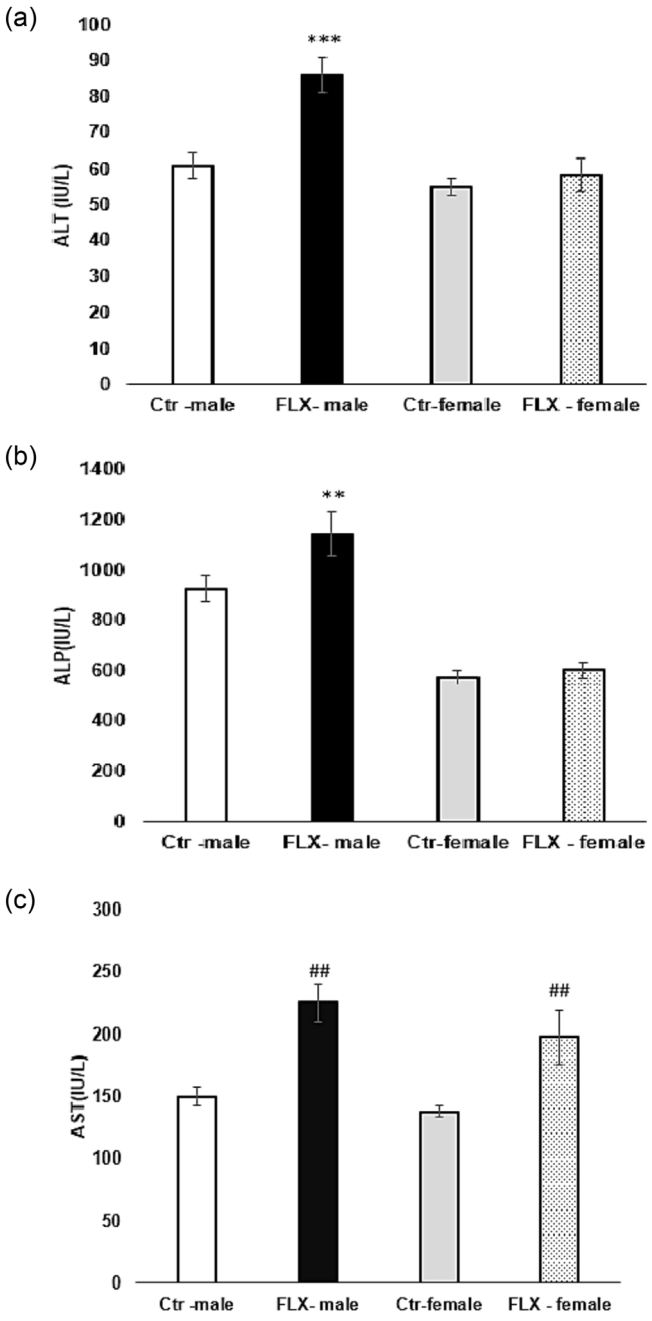

FIGURE 1 The effects of FLX administration during adolescence on hepatic enzyme level. FLX significantly increased serum alanine aminotransferase (ALT) (a) and alkaline phosphatase (ALP) (b) in males in comparison with the other groups. The aspartate aminotransferase (AST) level (C) was raised in FLX-treated male and female rats compared to the control groups. $^{**}P < 0.01$ and $^{***}P < 0.001$ versus other groups. $^{\#\#}P < 0.01$ in comparison with the control group.

3 | RESULTS

3.1 | The effects of treatment with FLX during adolescence on hepatic enzyme level

The two-way analysis indicated a significant interaction between sex and treatment on the serum level of ALT ($F[3, 28] = 12.916$, $p < 0.001$), ALP ($F[3, 28] = 27.566$, $p < 0.001$), and AST ($F[3, 28] = 8.450$, $p < 0.001$). FLX significantly increased serum ALT and ALP in males ($p < 0.001$ and $p < 0.01$, respectively) in comparison with the other groups (Figure 1a,b). The AST level was raised in both male and female-treated rats ($p = 0.001$ and $p = 0.004$, respectively) as compared with the control groups (Figure 1c).

3.2 | Hepatic side effects of FLX administration during adolescence

The histopathological study showed that the hepatic plates and sinusoids were uniformly arranged in the control groups (Figure 2a,b) (Figure 3a–c). However, hepatic plates were more seriously affected, and the sinusoids were irregular in adolescent FLX-treated male rats (Figure 2c–f). The portal triad was severely infiltrated by lymphocytes in male liver slides (Figure 2c). Degenerative changes including hepatocytes' non-uniform shape, irregular cytoplasmic borders, and foamy appearance were observed especially on the 1st and 2nd zones of FLX-treated male rats (Figure 2e,f). The central vein of hepatic lobules was congested, and red blood cells were accumulated in most of them (Figure 2d,f). A higher number of kupffer cells were detected in the sinusoid of treated male rats. There was no significant increase in fibrosis or collagen deposition in the parenchyma or portal area of FLX-received male rats (Figure 2a–f). Minimum or nearly normal changes were observed in female liver slides (Figure 3a–f). Lymphocyte infiltration was detected in some of the portal triads of female livers (Figure 3f).

3.3 | Adverse effects of FLX on cardiac structure in male and female rats

Our results indicated that the weight of the heart was greater in FLX-treated male ($p = 0.017$) and female ($p < 0.001$) groups in comparison with control groups (Figure 4a,b). The relative wall thickness of the right

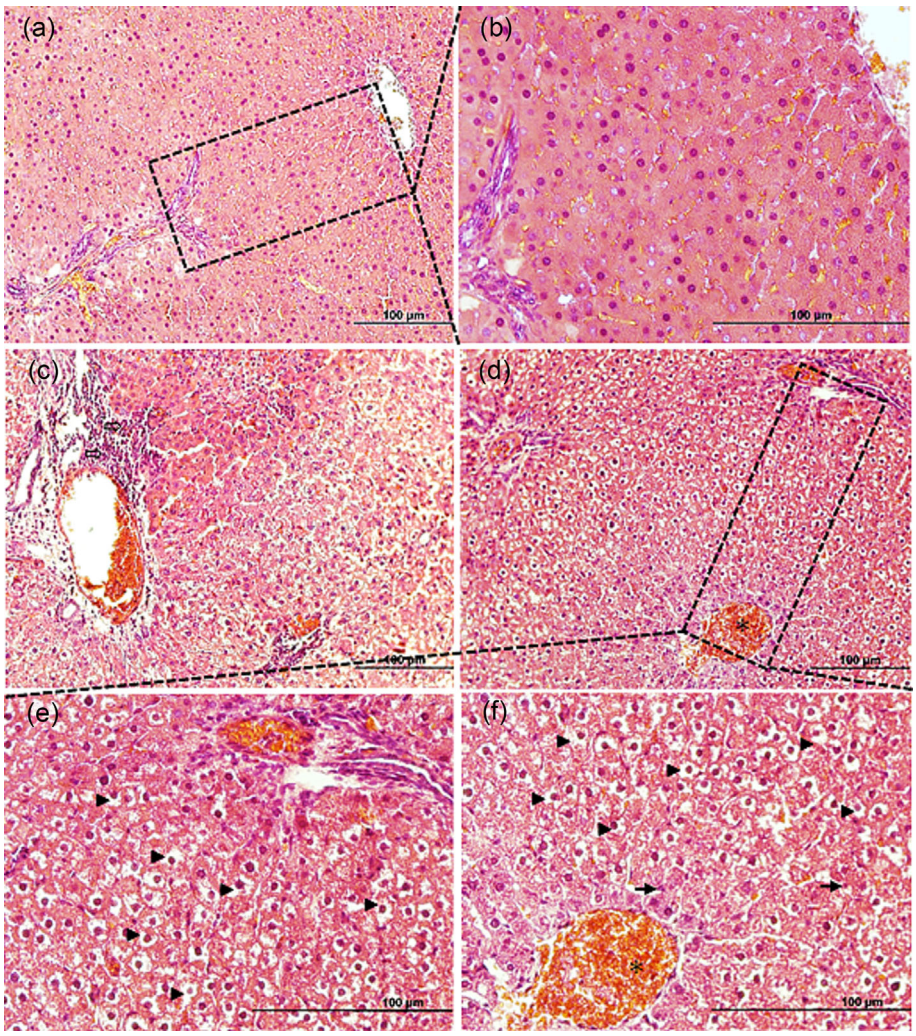

FIGURE 2 Treatment with FLX adversely affects adolescent male rat liver. Normal distribution of hepatic plates and sinusoids in the control group were shown in (a) and with higher magnification of the boxed area in (b). (c–f) FLX-treated liver slides. Hollow arrows in (c) demonstrate the higher number of lymphatic infiltrations in the portal triad. Degenerative changes in hepatic zones are shown in (d) and with higher magnification of the boxed area in (e) and (f). Arrowheads demonstrate the degenerative changes in some of the hepatocytes. Arrows and asterisks indicate the kupffer cells and the central veins of hepatic lobules, respectively.

and left ventricles was higher in FLX-treated male ($p = 0.005$ and $p = 0.001$, respectively) and female ($p < 0.001$) rats compared to the control groups (Figure 5a–e).

4 | DISCUSSION

Our study assessed the effects of FLX exposure during adolescence on the cardiac and hepatic system structure. Since the hepatic system is a primary organ for drug activation, detoxification, and lipid metabolism, we investigated the effects of chronic administration of FLX on liver injury via enzymatic and histopathological assessments. Our results revealed that treatment with FLX increases the serum level of ALP, and ALT in males, and AST in both sexes. In agreement with our study, it has been demonstrated that FLX treatment increases the levels of carbonyl groups, thiobarbituric acid reactive species, and the uric acid content in the liver. The ALT, AST, and glutathione-S transferase activities increased in the serum of the FLX-treated groups.[9] FLX causes a significant abnormality in hepatic catalase (CAT), superoxide dismutase activities, vitamin C levels, and serum biochemical parameters in rats.[23] The results of a previous experimental study indicated a significant increase in serum triglyceride (TG), cholesterol, and low-density lipoprotein levels in FLX-treated patients. In the same way, FLX altered the expression of lipogenic and lipolytic enzymes and elevated the TG level in the liver tissues of depressed mice. These changes are associated with disorders of lipid metabolism induced by FLX treatment.[24] Furthermore, abdominal obesity and hypercholesterolemia were associated with FLX treatment.[25] It has been pointed out that FLX administration induces hepatic lipid accumulation through the promotion of lipogenesis and reduction of lipolysis in the primary mouse hepatocytes. This study specifically states that FLX consumption inhibits carboxylesterases, which may explain the link of FLX to an increase in lipid accumulation.[12] FLX induces hepatotoxicity and elevated serum malondialdehyde, protein carbonyl, lipid profile, ALT, AST, ALP, and total bilirubin in Wistar rats.[26]

Our histopathological data indicated that FLX administration during adolescence more seriously

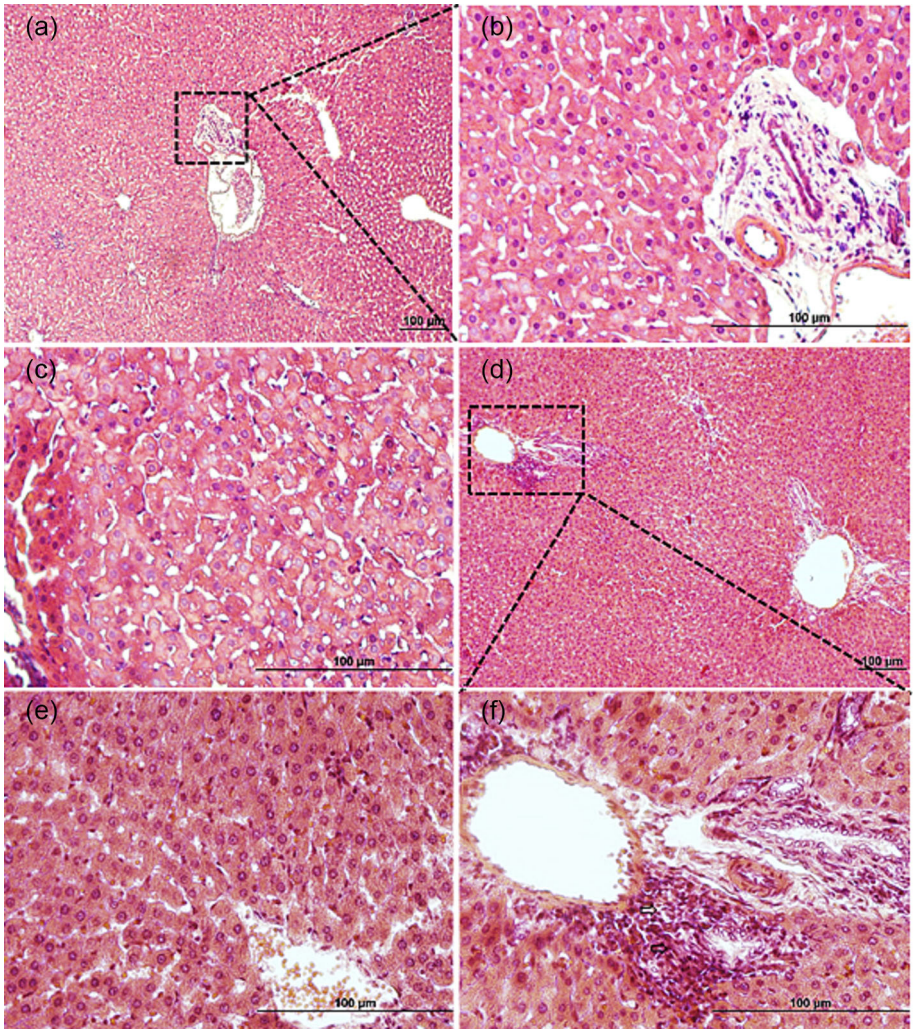

FIGURE 3 Treatment with FLX follows with minimum changes in adolescent female liver slides. (a–c and d–f) The control and FLX-treated female rat liver slides in low and high magnifications, respectively. Hollow arrows in (f) demonstrate the higher number of lymphatic infiltrations in the portal triad of FLX-treated rat.

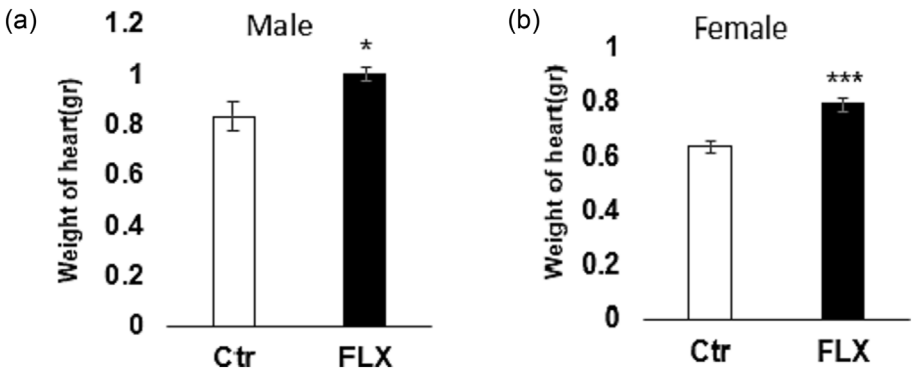

FIGURE 4 Treatment with FLX during adolescence increases heart weight. The total weight of the heart was increased in FLX-treated male (a) and female (b) rats. $^{*}P < 0.05$ and $^{***}P < 0.001$ versus other groups.

affects the hepatic system of male rats and causes irregular sinusoid manifestations. The portal triad was severely infiltrated by lymphocytes in the male liver slide. Degenerative changes were observed especially in the 1st and 2nd zones of FLX-treated male rats. A higher number of kupffer cells were observed in the sinusoid of treated male rats. In agreement with our study, it has been demonstrated that FLX administration leads to hepatotoxicity, hydropic degeneration, karyomegaly, lobular inflammation, focal necrosis, apoptosis, portal area inflammation, kupffer cell hyperplasia, and double nuclei in hepatic cells.[27]

The findings of the present study also showed that treatment with FLX affects the hepatic system of male rats in comparison with the female animals. There are considerable differences in the pharmacokinetic profile of males and females. Differences in the metabolism and distribution of antidepressants and the presence of

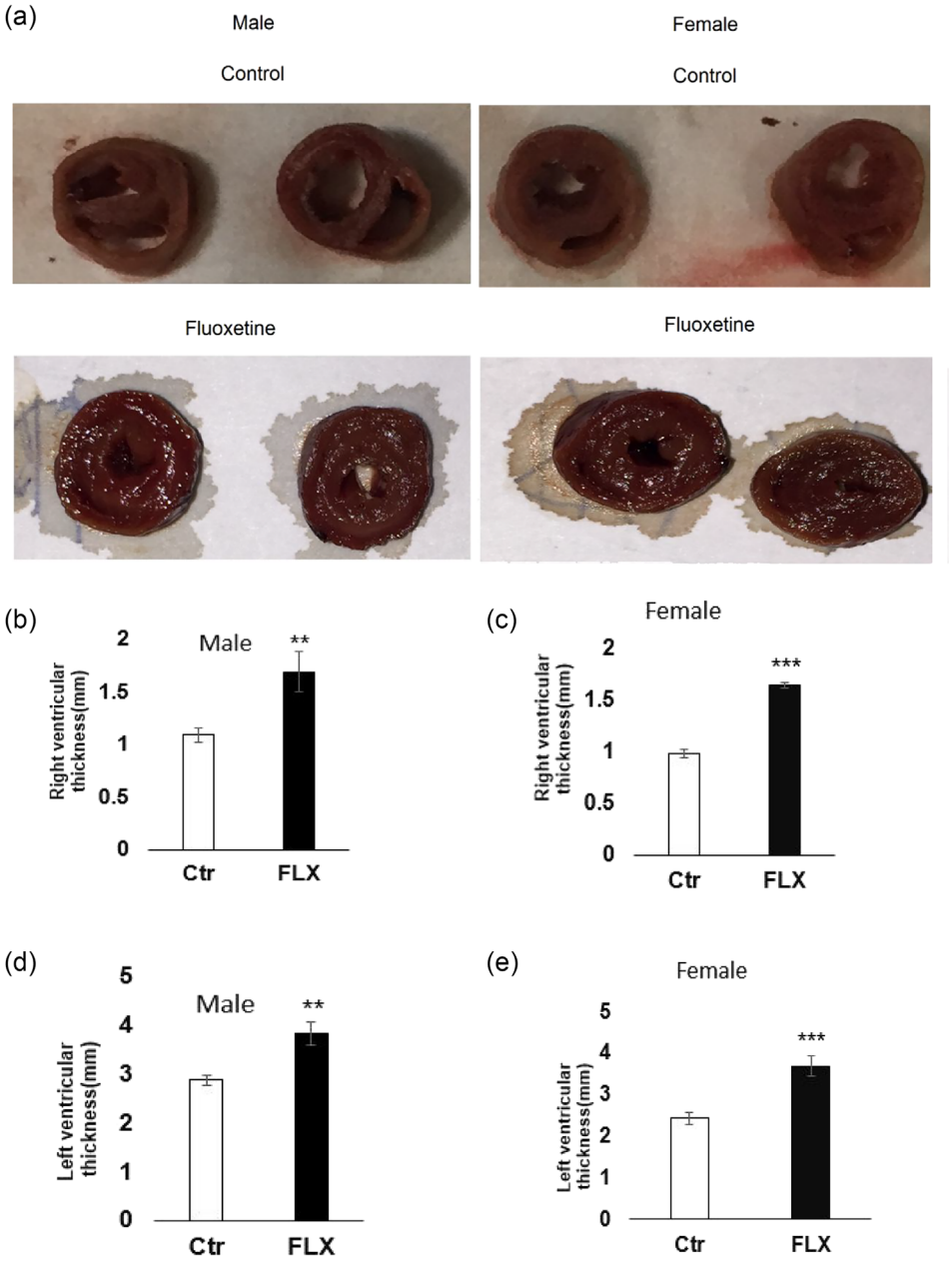

FIGURE 5 Treatment with FLX during adolescence induces right and left ventricular hypertrophy in male and female rats. The relative wall thickness of the right (b, d) and left ventricles (c, e) was higher in FLX-treated male and female rats compared to the control groups. $^{**}P < 0.01$ and $^{***}P < 0.001$ versus control group.

estrogen in females may have therapeutic effects on the occurrence of side effects.[28] Estrogen levels may have a clinical effect on the metabolism of antidepressants. It has been shown that the female sex hormone is a substrate for several cytochrome P450 enzymes.[28,29] In addition, estrogen can decrease hepatic metabolism because of changes in hepatic blood flow.[30]

In the present study, we also assessed the side effects of FLX on the cardiac system. The findings of our work indicated that FLX treatment during adolescence resulted in an increase in weight and wall thickness of the right and left ventricles in male and female rats, especially in female animals. Reviewing the literature indicates that chronic use of selective serotonin reuptake inhibitors (SSRIs) leads to right ventricular hypertrophy. In addition, cardiac arrhythmias, long QT syndrome, torsade de pointes, syncope, morphological changes in heart valves, and hypotension are related to SSRI treatment.[6] Nevertheless, inappropriate SSRI consumption may lead patients to more complicated treatments as a result of the antidepressants' side effects. Another study showed that chronic FLX treatment can increase plasma catecholamines, mild blood pressure, tachycardia, and baroreflex dysfunction in healthy rats, which may contribute to FLX-mediated sympathoexcitation and possibly parasympathetic depression. It was suggested that the cardiovascular autonomic effects of chronic FLX treatment may be of clinical importance. Treatment with FLX in depressed

geriatric patients has potential cardiovascular side effects because of age-related changes in pharmacokinetics in plasma concentrations of SSRIs and its active metabolite, norfluoxetine.[13] The development of mild hypertension after FLX treatment has been reported in rats.[31] Also, there is a case report of fluoxetine-induced systemic hypertension in children and adolescents.[7] These cardiovascular effects would be the central effects of FLX on the brain's serotonergic system.[32]

In conclusion, the present study provides evidence in our perception of the cardiac and hepatic adverse effects of FLX. Further studies are required to understand the underlying mechanisms of the observed impairments following FLX treatment.

AUTHOR CONTRIBUTIONS

Data collection: Hajar Babaaeyan, Farshid Sadegzadeh, and Nona Sakhaie. *Study design and manuscript writing*: Hakimeh Saadati and Ali Niapour. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethical committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1401.034).

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