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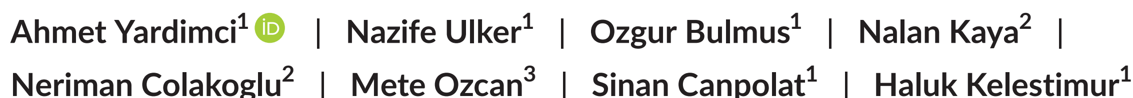
Effects of long-term paroxetine or bupropion treatment on puberty onset, reproductive and feeding parameters in adolescent male rats



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Abstract

Antidepressant use in adolescents has become more common in recent years. We have found several studies stating that prenatal antidepressant exposure can lead to delayed or earlier puberty onset but there was no study on postnatal paroxetine or bupropion. The main aim of this study was to investigate the effect of postnatal exposure to bupropion or paroxetine on puberty onset, reproductive and feeding results. The male rats (n = 8/group) aged 21 days were exposed to paroxetine (3.6 mg/kg) or bupropion (17 mg/kg) orally by gastric gavage every day from postnatal day 21–90. Also, control group received only saline orally as a vehicle. Postnatal exposure to bupropion or paroxetine delayed puberty onset compared to control group, but it was not significant. Sperm counts were significantly lower in the paroxetine and bupropion groups compared to control group. Sperm motility was significantly lower in only bupropion group. In addition, sperm motility was lower in paroxetine group, but it was not significant. In the histopathological examination, there was damage to the testicular structure in both treatments. Taken together, our result indicates that postnatal paroxetine or bupropion exposure may affect puberty onset and contribute to the impairment in fertility in male rats.

KEYWORDS
bupropion, FSH, LH, paroxetine, puberty

1 | INTRODUCTION

Puberty is a developmental period associated with significant somatic and behavioural changes, where adequate reproductive capacity is reached and the gonadal axis is fully awakened (Roa et al., 2010). The age of puberty can vary depending on factors such as race, gender, genetic, nutrition, living conditions and secular trends (Ercan, 2005; Parent et al., 2003). With the development of living conditions and socioeconomic status in many countries around the world, it was reported that the age of menarche comes to earlier to an average of 3.6 months per 10 years in every 100 years (Keizer-Schrama & Mul, 2001; Ong, Ahmed, & Dunger, 2006). It is thought that these changes occurred in the onset of puberty due to the secular trends are caused by postnatal environmental factors (Domine, Parent, Rasier, Lebrethon, & Bourguignon, 2006). We think that one of these factors may be antidepressants because antidepressant use in children and adolescents has increased significantly in recent years (Bachmann et al., 2016). In addition, it was reported that before adolescence (<12 years of age), boys took more prescribed antidepressant drugs than girls (O'Sullivan et al., 2015). Whether or not postnatal antidepressants' use can lead to precocious or delayed puberty is almost unknown.

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Selective serotonin reuptake inhibitors (SSRIs), including paroxetine, are the most widely used antidepressants in the world (Krasowska, Szymanek, Schwartz, & Myśliński, 2007). They increase the level of extracellular serotonin (5-hydroxytryptamine, 5-HT) by inhibition of 5-HT reuptake. This effect is thought to be the main mechanism, and how they show exactly their effects is not known yet (Sanchez, Reines, & Montgomery, 2014). Increases in 5-HT levels in some specific regions of the brain allow the SSRIs to demonstrate therapeutic properties. However, the effect of SSRIs on the 5-HT transporter is not specific to a certain brain region. They increase 5-HT levels in many regions of the nervous system. As a result, some side effects occur (Carrasco & Sandner, 2005). In regard to these antidepressants' effects on the puberty onset, there are few studies about only prenatal treatment (dos Santos et al., 2016; Moore et al., 2015).

In regard to bupropion, it is used in the treatment of depression and some psychiatric disorders (Fava et al., 2005). It is known that bupropion shows its antidepressant effect by inhibiting dopamine and norepinephrine reuptake (Belson & Kelley, 2002; Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006). It is also the only antidepressant with double effect on norepinephrine–dopamine. Whether or not there is a serotonergic activity is not known yet (Demyttenaere & Jaspers, 2008). Unlike many other antidepressants, bupropion does not cause weight gain and even provides weight loss (Fava et al., 2005). There is only one study about the effects of prenatal bupropion treatment on the puberty onset (De Long et al., 2013). However, postnatal effects of paroxetine or bupropion treatment on the puberty onset are almost unknown.

The main aim of this study was to determine the effects of postnatal long-term paroxetine or bupropion treatment on the puberty onset and reproductive parameters.

2 | MATERIALS AND METHODS

2.1 | Animals and treatments

Twenty-four (21 days of age) male Sprague-Dawley rats, weighing 40 ± 2 g, were obtained from the University of Firat Experimental Research Unit (FUDAM). This study was done at FUDAM in compliance with the guidelines for the ethical use of laboratory animals that were approved by the Firat University Ethic's Committee of Experimental Animals Research as of 11.06.2014, number 140 (Elazig, Turkey). The rats were individually housed in standard cages for 12:12-hr light-dark cycles with constant temperature (21 ± 1°C) and humidity (55 ± 5%). Pelleted food and tap water were provided ad libitum. Changes in food and water consumption and body weights of animals were recorded between 10.00 and 12.00 a.m. each day for 69 days. The groups were determined as control, paroxetine and bupropion groups (n = 8 in each group). Paxil tablets containing 20 mg paroxetine (SmithKline Beecham Pharmaceuticals, UK) and Wellbutrin XL (Aspen Bad Oldesloe GmbH in Bad Oldesloe, Germany) containing 150 mg bupropion were supplied from a local pharmacy. The required amount of paroxetine and bupropion was crushed in mortar separately and solved in saline. Both antidepressants were prepared just before treatment. Paroxetine (3.6 mg/kg) and bupropion (17 mg/kg) were given orally by gastric gavage between 10.00 and 12.00 a.m. every day from postnatal day (pnd) 21 (weaning day) to pnd 90. In addition, control group received only saline as a vehicle. Both drugs' doses were effective doses for rats and, based on previous studies (Inass, Hassan, Fouad, & El-Komey, 2005; Terry & Katz, 1997) and tablet form of both drugs, were used to mimic the administration way in humans. In addition, in order to determine puberty onset age of animals, we assessed preputial separation, morphological signs of the puberty in male rats, from pnd 30 to puberty. The experiment finished at pnd 90. At the end of the study, the animals were first anesthetised with 60 mg/kg ketamine and 5 mg/kg xylazine cocktail intramuscularly and were placed in supine position. Then, the abdomen was opened by incision and 5-ml blood sample was taken from abdominal aorta to blood tubes for hormone analyses and then centrifuged at 1792 g for 5 min at +4°C. Serum samples were stored in −20°C until the luteinising hormone (LH), follicle-stimulating hormone (FSH), leptin and testosterone ELISA were performed.

2.2 | Reproductive organs weights

After opening the abdomen by incision, left and right epididymis, testicular tissues, prostate and seminal gland were taken respectively. In order to prevent the loss of motility, the left epididymis was first weighed, and then, the other reproductive organs were weighed as wet, and the data were recorded. Finally, the animals were then decapitated and the procedure terminated.

2.3 | Epididymal sperm analyses

All sperm analyses were performed using the methods reported in the previous study (Turk et al., 2008). The epididymal sperm concentration was determined by a hemacytometer using a modified method. The right epididymis was finely chopped in a petri dish in 1 ml saline with the aid of a scalpel. It was then completely crushed with a tweezers for 2 min and then incubated for 4 hr at room temperature to allow all spermatozoa to pass from the epididymal tissue to the fluid. After incubation, the epididymal tissue-fluid mixture was filtered through a strainer to separate the supernatant from the tissue particles. The supernatant fluid containing all epididymal spermatozoa was drawn into the capillary tube until line 0.5 of the pipette designed to count the red blood cells. The solution containing 0.595 M sodium bicarbonate, 1% formalin and 0.025% eosin was drawn into the bulb up to 101 lines of the pipette. The contents of the pipette were mixed. Sufficient solution was then blown from the pipette to ensure that the diluents containing no spermatozoa were flushed from the capillary. This gave a dilution rate of 1:200 in this solution. Approximately 10 ml of the diluted sperm suspension was transferred to both counting chambers of an Improved Neubauer (Deep 1/10 mm; LABART, Darmstadt, Germany) and allowed to stand for 5 min. The sperm cells in both chambers were counted with a light microscope at

TABLE 1 Effects of paroxetine or bupropion on male rats' puberty onset age

Groups	Puberty onset age (day)
Control	47.12 ± 0.91
Paroxetine	50.75 ± 1.63
Bupropion	49.87 ± 1.10

Note. One-way ANOVA and post hoc Tukey's HSD tests were used for evaluation of the data. Data are represented as mean ± *SEM*.

200× magnification. The percentage of forward progressive sperm motility was assessed using a light microscope with a heated stage. For this process, a slide was placed on a light microscope with a heated stage warmed up to 37°C, and then, several droplets of Tris buffer solution (0.3 M Tris(hydroxymethyl)aminomethane, 0.027 M glucose, 0.1 M citric acid) were dropped on the slide and a very small droplet of fluid obtained from left cauda epididymis with a pipette was added to the Tris buffer solution and mixed by a cover-slip. The percentage of forward progressive sperm motility was assessed visually at 400× magnification. Motility estimates were conducted from three different fields in each sample. The mean of the three successive estimations was used as the final motility score. In order to determine the percentage of morphologically abnormal spermatozoa, the slides stained with eosinenigrosin (1.67% eosin, 10% nigrosin and 0.1 M sodium citrate) were prepared. The slides were then viewed under a light microscope at 400× magnification. A total of 300 sperm cells was examined on each slide (2,400 cells in each group), and the head, tail and total abnormality rates of spermatozoa were expressed as a percentage.

2.4 | Histopathological examination

After decapitation, testis tissues were fixed in Bouin's solution. Tissues were embedded in paraffin by applying routine tissue preparation techniques. The 5-µm-thick tissue sections were taken from paraffin blocks, and then, tissues were stained by periodic acid–Schiff (PAS) technique. All of tissue sections were examined and photographed by Olympus BH2 photo-microscope. Histopathological changes were revealed by counting them on randomly selected twenty areas at 20× magnification for each group.

2.5 | Hormone measurements

Serum FSH and LH hormone levels were determined by ELISA, based on the method reported by a previous study with some modifications (Pappa, Seferiadis, Marselos, Tsolas, & Messinis, 1999). Initially, pre-incubation was made with standards and serum samples in the 96-well plates (Nunc, Roskilde, Denmark), coated with rat LH and FSH antibodies, and antigen binding was achieved with primary antibodies at solid phase. Washing was then carried out on the plates, and secondary antibody-conjugated streptavidin was added to each well and colour formation was achieved using tetramethylbenzidine as the substrate. After incubation, the plates were assayed at 450 nm in ELISA (Biotek, Synergy HT, USA). Rat FSH and LH primary antibodies (rabbit anti-rat LH and rabbit anti-rat FSH) were supplied from Dr. AF Parlow (National Institute of Diabetes and Digestive and Kidney Diseases National Hormone and Peptide Program, National Institutes of Health, USA). Secondary antibodies (goat anti-rabbit IgG) and its conjugate streptavidin peroxidase were purchased from Sigma (Sigma-Aldrich, Taufkirchen, Germany). The inter- and intra-assay variation coefficients for both LH and FSH were <8%. Leptin and testosterone ELISA kits were supplied from the YH Biosearch Laboratory (Shanghai, China). In leptin analysis, serum samples were first incubated with leptin monoclonal antibodies previously added to the plates. Biotin-linked anti-LEP antibodies were then added to the wells, and coupling with streptavidin–HRP was achieved. After incubation, washing was carried out, and colour formation was accomplished by the addition of substrates A and B. The same procedure was repeated for testosterone measurement. After incubation, the plates were assayed at 450 nm in ELISA (Thermo Scientific, USA). The sensitivity of the measurement to leptin was 0.05 ng/ml and 0.25 nmol/L for testosterone. The inter-assay variation coefficients for both leptin and testosterone were below 12%, and the intra-assay variation coefficients were below 10%.

2.6 | Statistical analysis

All values were expressed as mean ± standard error of mean (*SEM*). Statistical analyses and graphs were as follows: SPSS 21.0 and Origin 6.0. One-way ANOVA post hoc Tukey's HSD and Pearson's chi-square tests were used for evaluation of the data. In all analyses, $p < 0.05$ was considered statistically significant.

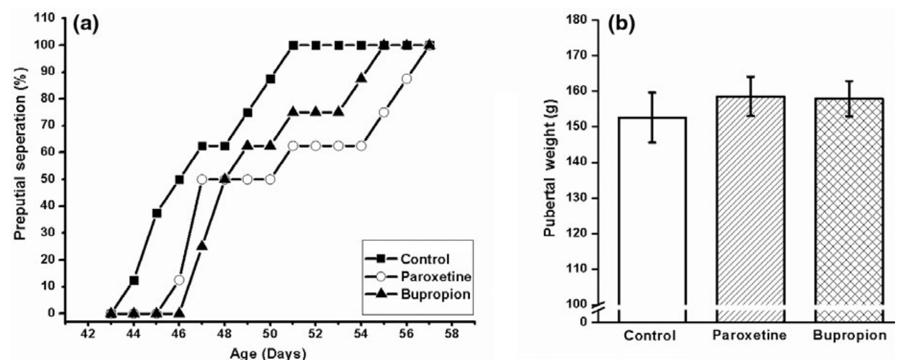

FIGURE 1 Effects of paroxetine or bupropion on puberty onset are documented in male rats (pnd 21–90). (a) Preputial separation and (b) pubertal weights are presented for animals treated with paroxetine or bupropion (one-way ANOVA followed by post hoc Tukey's HSD test). $n = 8$ for each group

TABLE 2 Effects of paroxetine or bupropion on male rats' reproductive organs' weights

Variable	Control	Paroxetine	Bupropion
Testis (mg)	1037 ± 62.31	993.7 ± 31.89	860.4 ± 51.96
Epididymis (mg)	342.5 ± 12.48	322.9 ± 14.62	363.9 ± 14.83
Prostate (mg)	107.8 ± 10.82	94 ± 8.73	98.5 ± 3.98
Seminal vesicle (mg)	303.1 ± 19.67	281 ± 9.29	295.1 ± 11.55

Note. One-way ANOVA and post hoc Tukey's HSD tests were used for evaluation of the data. Data are represented as mean ± *SEM*. $n = 8$ for each group.

3 | RESULTS

3.1 | Effects of paroxetine or bupropion on puberty parameters and reproductive organs

Treatment of paroxetine or bupropion caused the puberty onset a slight shift from 47.12 ± 0.91 to 50.75 ± 1.63 and 49.87 ± 1.10 days respectively. However, the extents of puberty timing were not significant (Table 1). While all of the animals in control showed complete preputial separation on 51 days, animals treated with paroxetine or bupropion presented complete preputial separation at 57 days and 55 days, respectively, and there was a shift towards to the right in puberty onset day (Figure 1a). The starting days of puberty onset were 44 days in the control group, 46 days in the paroxetine group and 47 days in the bupropion group, and pubertal weights were not changed by bupropion or paroxetine treatment (Figure 1b). Also, there was no statistically significant difference in testis, epididymis, prostate and seminal vesicle weights (Table 2).

3.2 | Effects of paroxetine or bupropion on LH, FSH, testosterone and leptin levels

Treatment of bupropion caused a significant rise in LH levels (3.66 ± 0.1 vs. 2.73 ± 0.1 for the control group, $p < 0.01$; Figure 2a). However, the LH value of the paroxetine (2.87 ± 0.1 vs. 2.73 ± 0.1) group was not statistically significant compared with the control group. In addition, there was no statistically significant difference between the control group and other groups at FSH levels (Figure 2b). The testosterone levels were 39.69 ± 2.27 for the control group. Bupropion group (47.74 ± 2.33) was found to be significantly increased compared to the control group in testosterone levels ($p < 0.05$; Figure 2c). There was no significant difference between the paroxetine group (43.35 ± 1.60) and the control group in testosterone levels (Figure 2c). Also, leptin levels were not changed by paroxetine or bupropion treatment (Figure 2d).

3.3 | Effects of paroxetine or bupropion on sperm parameters

In the rats administered paroxetine or bupropion, cauda epididymal sperm count was significantly lower in both treatment groups

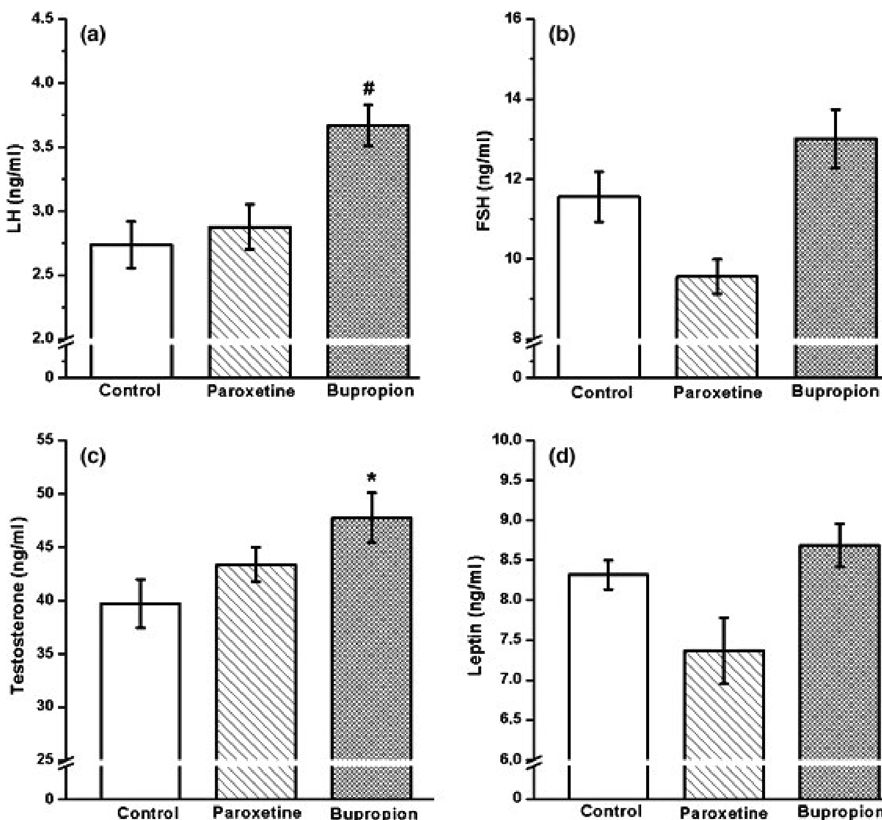

FIGURE 2 Effects of paroxetine or bupropion on (a) LH levels, (b) FSH levels, (c) testosterone levels and (d) leptin levels in male rats. *$p < 0.05$; versus control group, $^{\#}p < 0.01$; versus control group (one-way ANOVA followed by post hoc Tukey's HSD test). $n = 8$ for each group

TABLE 3 Effects of paroxetine or bupropion on male rats' sperm parameters

Variable	Control	Paroxetine	Bupropion
Sperm concentration (×10^6/ml)	107.25 ± 7.09	42 ± 7.12*	38 ± 6.32*
Sperm motility (%)	80 ± 1.88	73.75 ± 3.75	64.28 ± 4.80**
Sperm morphology (%)			
Normal	76	60	52
Abnormal-total (tail + head)	24	40**	48*

Notes. Pearson's chi-square test was used for evaluation of sperm morphology data. One-way ANOVA and post hoc Tukey's HSD tests were used for evaluation of the other data. Data are represented as mean ± *SEM*.
*$p < 0.001$, **$p < 0.05$; significantly different than control. $n = 8$ for each group.

compared with the control group (42 ± 7.12 and 38 ± 6.32 vs. 107.25 ± 7.09 × 10^6/ml, respectively, $p < 0.001$). Also, sperm motility was significantly lower in the bupropion group (64.28 ± 4.80 vs. 80 ± 1.88% for the control group, $p < 0.05$). The effects of paroxetine or bupropion on sperm parameters are presented in Table 3.

3.4 | Effects of paroxetine or bupropion on food and water intake and body weight

There was no statistically significant difference between the control group and other groups at food (Figure 3a) and water intake (Figure 3b) in the 69-day period. However, in the paroxetine group

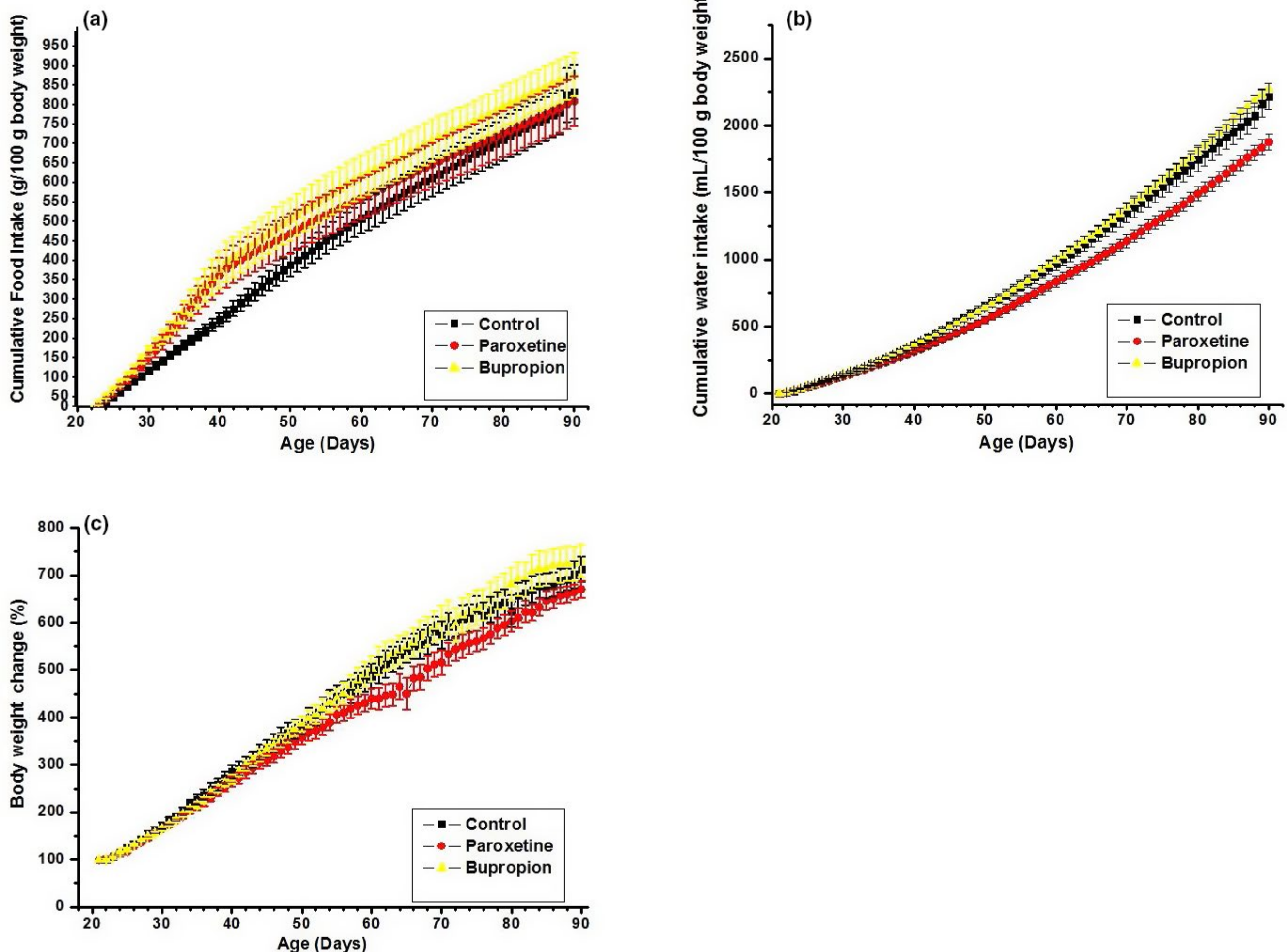

FIGURE 3 Effects of paroxetine or bupropion on different indices of energy balance documented in male rats (21–90 days). (a) Food intake, (b) water intake and (c) body weight change (%) (one-way ANOVA followed by post hoc Tukey's HSD test). $n = 8$ for each group

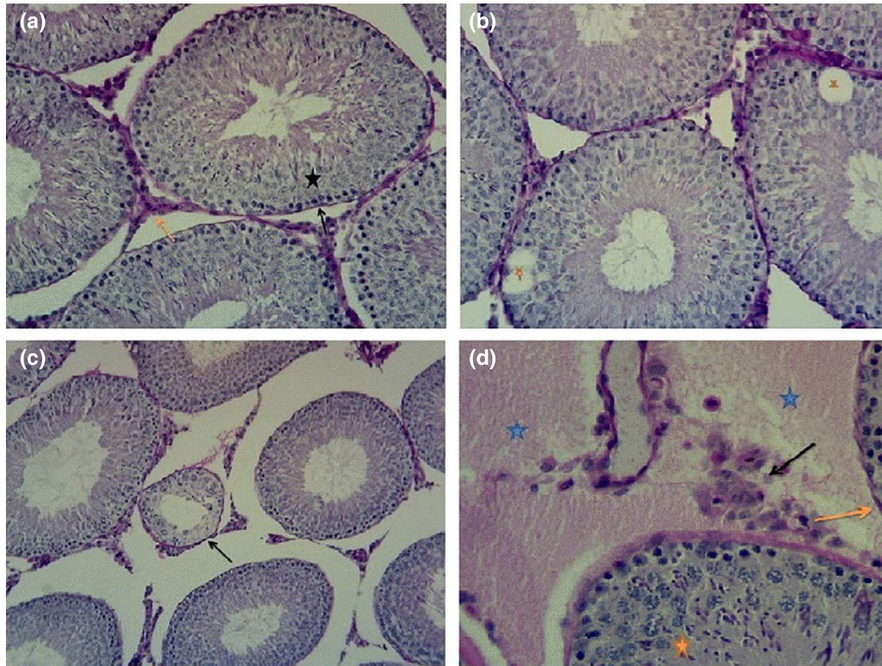

FIGURE 4 Histological illustration of testicular tissues in rats with paroxetine or bupropion treatment. (a) Control group: Spermatogenic series cells (black star) and Sertoli cells, basal membrane (black arrow) and interstitial Leydig cells (orange arrow) are distinguished in their normal structure. (b, c) Paroxetine group: Seminiferous tubule basal membrane and Leydig cells are normal, but vacuolisation (orange star) is distinguished in the seminiferous tubule epithelium and atrophic seminiferous tubule structure (arrow) among the normal-appearanced seminiferous tubules. (d) Bupropion group: Seminiferous tubule epithelium (orange star), basal membrane structure (orange arrow) and Leydig cells (black arrow) are observed normally, while prominent interstitial oedema (blue star) is noteworthy. Periodic acid–Schiff (PAS) with haematoxylin counterstained Mag. 200×

food intake, it was determined that there was an increase in the levels of pnd 25 to the pnd 40, although it was not significant, and was similar to the control group values after pnd 40. In the 69-day period, bupropion food intake values were observed in parallel with the control group (Figure 3a). For the water intake, it was found that bupropion group values were similar to the control group. In the paroxetine group, there was no statistically significant difference in the 69-day period compared to the control group in water intake (Figure 3b). Similarly, there was no statistically significant difference between the control group and other groups at body weight change for 69-day period (Figure 3c).

3.5 | Effects of paroxetine or bupropion on histopathology of testicular tissue

As a result of examination of testicular tissues in the light microscope, it was determined that there were some differences in the testicular tissue in all groups compared to the control group. In the sections of the control group, seminiferous tubule structure, Sertoli cells and interstitial Leydig cells were normal (Figure 4a). When the paroxetine and bupropion groups were evaluated, it was seen that there were atrophy in the seminiferous tubules, oedema in the interstitial area of seminiferous tubules and vacuolisation in the seminiferous tubules epithelium in both groups. Among these changes, only interstitial oedema is statistically significant at only bupropion group ($p < 0.05$). Histological damage scores for treatment groups are presented in Table 4.

4 | DISCUSSION

Puberty refers to the physical and psychological transition to adulthood as a result of changes in the activation of the hypothalamus pituitary gonadal (HPG) axis. These changes occur as a result of activation in all major elements, including hypothalamus, pituitary and gonads (Bianco, 2012). This period starts with the maturation of HPG axis; continues with phenotypic changes specific to the sex, growth of the muscles, bones and sexual organs; and ends with the

TABLE 4 Histological damage scores for rat exposed to paroxetine or bupropion compared with control

Groups	Interstitial oedema	Vacuolisation	Atrophy
Control	0.15 ± 0.08	0.2 ± 0.09	0.05 ± 0.05
Paroxetine	0.35 ± 0.11	0.55 ± 0.14	0.2 ± 0.09
Bupropion	0.6 ± 0.2*	0.45 ± 0.11	0.15 ± 0.08

Notes. One-way ANOVA and post hoc Tukey's HSD tests were used for evaluation of the data. Data are represented as mean ± *SEM*. $n = 20$ for each group.
*$p < 0.05$; significantly different than control.

achievement of full reproduction capacity (Gonc, 2009). Our study was the first to show that postnatal long-term exposure to the SSRI paroxetine or bupropion led to a delay slightly in male rats' puberty onset. Paroxetine treatment also did not result in any changes in pubertal weight, FSH, LH and leptin levels. However, bupropion treatment increased LH and testosterone levels significantly but did not change FSH and leptin levels. Neither paroxetine nor bupropion did not change water and food intake, body weight and reproductive organs weights. Also, paroxetine and bupropion treatment decreased sperm count and resulted in rise in abnormal sperm rate and histopathological changes in testicular tissue. In addition, sperm motility decreased only in bupropion treatment.

In relation to the effects of paroxetine treatment on the puberty onset, there has been only two prenatal SSRI treatment studies (dos Santos et al., 2016; Moore et al., 2015). In one of these studies, prenatal fluoxetine treatment did not change puberty onset and pubertal weight (Moore et al., 2015). However, in another study, prenatal and lactational exposure to fluoxetine delayed puberty onset in female rats (dos Santos et al., 2016). The effect of serotonin on the reproductive system is thought to be via the hypothalamus and the studies indicate the presence of synapses between serotonergic neurons and GnRH neurons. It is thought that a certain level of serotonin is needed to maintain the normal activity of the gonadal axis, and this is due to the facilitating effect of serotonin on the HPG axis. Another possibility is that serotonin acts as a stimulant or inhibitor with different serotonergic receptors on the HPG axis (Gore, 2002). Studies on the effects of 5-HT on GnRH secretion have been shown that 5-HT stimulates GnRH secretion by the activation of 5-HT_{2C}, 5-HT_4 and 5-HT_7 receptors and inhibits the activation of 5-HT_{1A} receptor (Moran et al., 2013). 5-HT can act as both stimulant and inhibitor of GnRH secretion due to sex and 5-HT receptor signalling pathways (Wada et al., 2006). In our study, paroxetine treatment caused a delay slightly in pubertal timing. Possibly, paroxetine increased 5-HT levels by its mechanism, and increased 5-HT might have acted as an inhibitor on pubertal timing. Interestingly, it seems that 5-HT has an inhibitor effect on GnRH in this study but testosterone and LH levels increased slightly; however, they are not significant. There is no mechanism of action to explain this paradoxal effect.

Similarly, postnatal bupropion treatment led to delay slightly in puberty onset and did not change pubertal weight. There was only one study about bupropion treatment but it was relevant to prenatal treatment. Bupropion exposure throughout pregnancy led to an advanced vaginal opening (i.e., earlier pubertal onset) in the female rats. Because of bupropion effects on dopamine transporter (DAT) as an inhibitor, hence, dopamine levels increase, and then, maternal care behaviour is affected negatively. As a result, puberty onset accelerates (De Long et al., 2013). In relation to the effects of postnatal bupropion treatment on puberty onset and pubertal weight, any mechanism of action does not exist. The timing of puberty has been identified as a crucial factor in mental health, with deviations from normative development placing an individual at greater risk of psychopathology. Recent studies suggested that deviations from the normative timing (i.e., either early or late maturation) are associated with negative results such as substance abuse, disruptive behaviour disorders and increased symptoms of depression (Cowan & Richardson, 2018). Consistent with our results, these situations indicate that exposure to paroxetine or bupropion during early life may cause disruptive alterations in adolescents' life.

5-HT regulates feeding behaviour through interaction between its various receptors. Serotonergic roles of presynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors on nutrition were investigated. 5-HT_{1B} and 5-HT_{2C} were thought to play a role in the formation of anorectic response by inhibiting feeding behaviour (Magalhaes et al., 2010). 5-HT_{1B} stimulation reduces neuropeptide Y (NPY)/agouti-related peptide (AgRP) neuronal activity and therefore tonic GABAergic inhibition of proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons, which in turn are activated by 5-HT_{2C} stimulation. These circuits synergistically contribute to the anorectic effects of serotonergic receptors in the hypothalamus (da Silva et al., 2019). In animal studies, it was suggested that chronic paroxetine treatment led to a decrease in body weight (Amodeo et al., 2015; de Jong et al., 2006; Konkle & Bielajew, 1999; Konkle, Sreter, Baker, & Bielajew, 2003). However, in this study, we reported that long-term paroxetine treatment did not lead to a significant change in body weight. Compatible with unchanged body weight values, there was also no significant change in food intake. It can be thought that low dose level (3.6 mg/kg) paroxetine could have not induced an anorectic response. If paroxetine treatment affected 5-$HT_{1B/2C}$ receptors, there would be a decrease in food intake. Thereby, also body weight would decrease. On the other hand, human studies suggest that chronic paroxetine treatment results in weight gain (Amodeo et al., 2015). The reason for this paradoxical effect is unknown.

It has been reported that bupropion does not cause an increase in body weight, and any significant changes in calorie intake, and appetite in studies on nutrition, and body energy condition (Demyttenaere & Jaspers, 2008). It has also been reported that it has no hypophagic effect (Liu, Connoley, Heal, & Stock, 2004). Compatible with this condition, in the present study, bupropion did not lead to any significant changes in body weight or food intake.

The secretion of antidiuretic hormone (ADH) in reply to osmotic stimuli is well reported but the neurotransmitter mechanisms that mediate these responses are less well understood. There is some evidence to offer that 5-HT has a physiological significance in osmoregulated ADH secretion since lesion of 5-HT cell bodies in the brain stem raphe nuclei blocks the normal increase in plasma ADH in response to water deprivation and to hyperosmotic infusion. Animal studies have reported that an acute rise in central 5-HT neurotransmission causes to a rise in plasma ADH (Faull, Charlton, Butler, & Baylis, 1993). In this study, paroxetine treatment caused a decrease in water intake although it was not statistically significant. As a result, it can be concluded that the increase in the levels of 5-HT due to paroxetine treatment might have stimulated the release of ADH and consequently decreased water intake.

Leptin, which plays an important role in puberty and reproduction, is a peptide produced mainly in white adipose tissue and transmits the peripheral adipose reserve information to the brain (Smeets, 2015). Leptin plays an important role in the regulation of energy homeostasis, neuroendocrine and immune functions, glucose and lipid metabolism (Park & Ahima, 2015). Studies have shown that the level of leptin is proportional to body fat and body mass index but many other factors are involved in the regulation of leptin (Frederich et al., 1995; Ma et al., 1996). In the present study, paroxetine or bupropion treatment also did not change leptin levels significantly. In studies performed on humans, it was determined that chronic paroxetine treatment had no effect on serum leptin levels (Hinze-Selch et al., 2000; Janssen, Touw, Schweitzer, & Waldinger, 2014; Ozsoy, Besirli, Abdulrezzak, & Basturk, 2014), but effects in rodents remained unknown. Bupropion also had no effect on leptin levels, and this situation was normal, because, as mentioned above, it has no hypophagic effect. Thereby, as food intake and body weight did not change, hence, leptin did not.

Spermatogenesis in mammals includes many events that occur in the HPG axis. The production of spermatozoa is regulated by the hormones luteinising hormone (LH) and follicle-stimulating hormone (FSH), which act on Leydig and Sertoli cells respectively. Both hormones are secreted in response to gonadotropin-releasing hormone (GnRH) production (Aragón et al., 2005). Sertoli cells are stimulated by secretion of FSH from the pituitary gland, and spermatogenesis occurs in germ cells at seminiferous tubules. As a result of LH secretion, Leydig cells are stimulated, and testosterone is synthesised. Therefore, LH, FSH and testosterone are used as markers of testicular activity and spermatogenesis in men. The anomalies or disorders in sperm production are manifested by distortions in sperm number and motility and may cause infertility (Sofikitis et al., 2008). 5-HT receptors are known to exist in the testis and epididymis, and they are responsible for regulating testicular blood flow in the testis and sperm maturation in epididymis. 5-HT receptors in Sertoli cells are thought to play a role in spermatogenesis (Syed, Gomez, & Hecht, 1999). Therefore, 5-HT may act on regulation of sperm motility and density. 5-HT induces corticotropin-releasing hormone (CRH) secretion via 5-HT_2 receptors in Leydig cells and stimulates phosphoinositol hydrolysis. As a result, an inhibitory effect on LH and testosterone secretion occurs (Frungieri et al., 1999). Also, it was suggested that SSRIs bind to the sulphydryl group in the sperm membrane and produce a spermicidal effect by interacting with phospholipids (Kumar et al., 2006). In addition, it has been reported that increased 5-HT levels have negative effects on semen parameters and may cause sperm dysfunction (Gonzales, Garcia-Hjarles, & Velasquez, 1992; Ortiz et al., 2010). Compatible with our results, in many studies, it was suggested that paroxetine and other some SSRIs can affect sperm parameters negatively (Bataineh & Daradka, 2007; Erdemir et al., 2014; Inass et al., 2005; Jahromy & Moghadam, 2014; Kumar et al., 2006). In some of these studies, it was reported that serum gonadotropin levels also decreased significantly with sperm parameters. However, there was no change in gonadotropins levels in our study. Some other studies have shown that SSRIs do not affect serum LH levels contrary to these results (Bell, Shipman, Bystritsky, & Haifley, 2006; Schlösser et al., 2000). We concluded that unchanged FSH and LH levels suggest that paroxetine treatment during juvenile development and adulthood does not alter HPG axis function but increased levels of 5-HT caused changes in sperm parameters and also testicular histopathology probably due to direct toxic effect of the paroxetine on the testes; hence, it can affect male fertility directly, because male factor infertility is usually diagnosed by the assessment of sperm concentration, sperm motility, and sperm morphology (Atli et al., 2017).

In a study, it was observed that serum LH levels increased, and FSH levels remained unchanged as a result of 30 days of chronic bupropion treatment (Cavariani et al., 2015). In a study conducted by Roshdy and Fyiad (2010), it was reported that chronic bupropion treatment caused a significant sperm anomaly in mice. Bupropion has been reported to adversely affect sperm motility. The loss of motility in the spermatozoa is closely related to productivity in men because it prevents the entry of spermatozoa into the oocyte. In vitro studies have shown that dopamine and adrenergic agonists stimulate chloride secretion with epididymal epithelial cells and that sympathetic innervation changes the epididymal fluid protein composition (Cavariani et al., 2015). Both factors are important factors in obtaining sperm motility and productivity. The loss of sperm motility in animals with bupropion treatment is thought to be caused by the modification of the epididymal ionic/protein luminal composition with sympathomimetic effect of bupropion. Although bupropion treatment revealed loss of sperm quality, it is known that bupropion has no effect on fertility in male rats. The decrease in sperm quality is thought to be masked by high reproductive activity in rats (Cavariani et al., 2015). In a study by Tanrikut and Schlegel (2007) on human effects, it was reported that bupropion treatment resulted in a decrease in sperm motility and number, and after the interruption of treatment, sperm concentration and motility values returned to normal. In the study performed by Kankash, Shariati, and Khatamsaz (2014), it was determined that serum LH and FSH levels increased significantly compared to the control group as a result of chronic bupropion treatment. Similarly, in the present study, bupropion treatment led to an increase in LH and testosterone levels. As mentioned above, bupropion shows its antidepressant effect by inhibiting dopamine and norepinephrine reuptake. Norepinephrine is thought to result in the formation of pulsatile GnRH secretion rather than controlling it (Herbison, 1997). The stimulation or inhibition of norepinephrine on the HPG axis depends entirely on steroids presence. In various studies, norepinephrine suppressed GnRH and LH secretion in ovariectomised rats but then regarding the progesterone/oestrogen treatment, it was observed that it stimulated in ovariectomised rats (Genazzani, Bernardi, Monteleone, Luisi, & Luisi, 2000). In the present study, probably bupropion led to an increase in norepinephrine levels. Increasing norepinephrine levels resulted in an increase in GnRH and then LH and finally testosterone levels. In addition, the increased serum LH levels that accompany the decreased sperm concentration and motility and increased abnormal sperm rate can be attributed to the compensatory mechanisms against this decrease

by inducing spermatogenesis by this hormone. Also, human studies have shown that serum LH levels have an inverse/negative correlation with sperm concentration (Atli et al., 2017).

In the histopathological examination, it was seen that there were atrophy in the seminiferous tubules, oedema in the interstitial area of seminiferous tubules and vacuolisation in the seminiferous tubules epithelium in both groups. Similarly, previously it was suggested that SSRIs may lead to the distortions in testicular tissue (Aggarwal, Jethani, Rohatgi, & Kalra, 2012; Atli et al., 2017; Yakubu & Atoyebi, 2018). It was reported that 5-HT plays a role on testis seminiferous tubules, accessory reproductive organs and epithelial cells by 5-HT receptor type-2 (5-HT 2R), and stimulates smooth muscle contraction. Therefore, it affects sperm production and maturation process. Excessive free 5-HT in the periphery perpetually induces the smooth muscle of blood vessels directly through 5-HT2R or indirectly by thromboxane A2. This effect may increase vasoconstriction and smooth muscle proliferation, leading to microcirculation distortions. 5-HT is known to be a powerful inflammatory mediator. High levels of 5-HT in the hypoxic conditions can stimulate testicular interstitial tissue inflammation and fibrosis, resulting in a decrease in blood supply and atrophy of Leydig cells (Aggarwal et al., 2012). We suggested that this atrophy might occur in seminiferous tubules indicated by another study (Atli et al., 2017). Also, in one study, paroxetine treatment-induced vacuole formation was reported (Inass et al., 2005). Together with the damages induced by paroxetine in the testicle, it is possible to associate degenerative findings detected in testicular tissue with the elevated 5-HT levels. In parallel with this result, sperm concentration decreased and sperm abnormal rate increased in paroxetine group. In relation to this result, it was reported that excess levels or absence of serotonin may cause disorders in sperm parameters (Atli et al., 2017).

In relation to the bupropion effects on the histopathology of testis, seminiferous tubule epithelium, basal membrane structure and Leydig cells were observed normally, while prominent interstitial oedema was noteworthy. Various studies have indicated that the levels of interstitial fluid can be increased by a variety of factors, such as endogenous LH (Porter, Shetty, & Meistrich, 2006). In our study, interstitial oedema may have occurred due to increased LH levels in bupropion group.

In summary, our study is the first to show that paroxetine or bupropion may lead to the delay in pubertal timing although both antidepressants did not alter body weight and food intake. The results derived from this study suggest that bupropion or paroxetine exposure during puberty may impair male reproduction in humans. However, this study is based on an animal model, and more clinical studies are needed in order to evaluate the effects of these antidepressants on puberty and reproductive parameters.

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