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RESEARCH

The effects of bupropion treatment on libido and hormones

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Abstract

As a dual dopamine and norepinephrine reuptake inhibitor, bupropion has received much attention for its effects, which increase sexual function and libido. This study was aimed at determining the potential effects of bupropion treatment on serum gonadal hormones, prolactin, and libido in dogs. The study animals comprised ten 2-year-old male dogs with a weak libido. The dogs were treated with 3 mg/kg of bupropion for 3 days. The serum testosterone, FSH, LH, and prolactin levels of the animals were measured before treatment and for a period of 4 weeks after treatment. The study groups were compared for their pre-treatment and post-treatment libido scores. According to the findings obtained in this study, no statistically significant change occurred in the serum testosterone, FSH, and prolactin levels of the dogs after receiving bupropion treatment. A statistically significant increase was detected in the serum LH levels measured throughout the 4-week period after treatment, when compared to the levels measured before treatment ($p < .05$). The libido scores did not differ between the pre-treatment and post-treatment periods. No increase having been determined in the post-treatment libido scores of the animals, despite their increased post-treatment LH levels, was attributed to either no increase having occurred in the testosterone levels of the animals or the specific dose and length of period they were administered with bupropion.

Keywords Bupropion · FSH · LH · Canine libido · Prolactin · Testosterone

Introduction

Male sexuality is affected by multiple factors, including among others, depression, anxiety, attraction, sexual functionality, cultural factors, sex roles, communication, and conflict. Adversities associated with these factors are considered to be the result of male sexual disinterest (Nimbi et al. 2020). Libido, defined as a condition reflecting the level of sexual interest at any given time, constitutes a fluctuating state of sexual motivation present in all organisms. Sexual motivation is influenced by both internal factors (circulating steroid hormone levels) and external factors (the presence of sexually relevant stimuli and reward) (Pfaus and Scepkowski 2005). Indicators of low libido in male dogs may include lack of interest in a female dog in estrus, failure to attempt mating despite sniffing the female, not assuming the mating position, or rejecting the female (Johnston et al. 2001). Exposure to aggressive or dominant male dogs during mating, encounters with older and more senior females, harsh discipline and erratic behavior by the owner, mating during the wrong heat time, and excessive sexual use are all causes of low libido in dogs. This condition can also occur in dogs that have previously been capable of mating (Mertens 2006; Cafazzo et al. 2014). In low libido and male hypogonadism, testosterone therapy is often preferred (Bhasin et al. 2018; Chung 2019; Salter and Mulhall 2019). Testosterone therapy can be administered via topical gel, intramuscular therapy, oral tablets, and patches. In addition, endocrinological conditions such as hyperprolactinemia, thyroid dysfunction, and diabetes should be excluded (Rubio-Aurioles and Bivalacqua 2013; Chung 2019).

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Antidepressants, the use of which is steadily increasing, are listed among factors known to cause sexual disinterest and sexual dysfunction (Clayton et al. 2014; Waldinger et al. 2015). Recent studies have shown that, despite being used more commonly in high-income countries compared to low-income countries, antidepressants are being used increasingly throughout the world (Kazdin et al. 2023). While earlier treatment protocols for depression were based on the use of conventional drugs such as tricyclic antidepressants and monoamine oxidase inhibitors, today, it is preferred to prescribe multi-indication drugs including selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) (Chen et al. 2021). SSRI may cause adverse effects such as diarrhea, stomachache, and stomach discomfort through their action on the gastrointestinal tract. Sexual adverse effects may frequently accompany these adversities (Waldinger et al. 2015). Similarly, SNRI also cause sexual dysfunction (Clayton et al. 2014). Sexual dysfunction caused by SSRI and SNRI may manifest as disorders related to libido, sexual arousal, erection, and orgasm (Clayton et al. 2014). As a result, all sexual phases (sexual interest, erectile function, arousal, and orgasm) can be affected (Csoka et al. 2008). Sexual dysfunction resulting from SSRI treatment may occur in response to a single particular administration dose of the drug (Williams et al. 2000). Medication-induced sexual dysfunction arises from SSRI increasing the synaptic concentrations of serotonin. Such an increase affects the tonus of smooth muscles responsible for sleep, arousal, appetite, sexual functions, and intestinal motility (Warden et al. 2010). Serotonin is reported to inhibit sexual function through its effects on sexual arousal and orgasm. These effects of serotonin are attributed to the disruption of dopamine levels and the decrease of nitric oxide synthesis (Meston and Frohlich 2000). It has been suggested that the serotonergic effects of SSRI and SNRI reduce dopaminergic transmission in the mesolimbic area and thereby negatively affect both orgasm and libido (Bella and Shamloul 2013). Dopamine is known to stimulate both sexual drive and desire. Furthermore, it facilitates penile erection by inducing the oxytocinergic neurons in the paraventricular center. The facilitating role of dopamine in erectile function and copulation behavior is known to be mediated mainly by dopamine receptors belonging to the D2 family (Melis et al. 2022). On the other hand, increased norepinephrine levels positively affect the stimulation of the sexual organs and orgasm through both central and peripheral actions. Thus, as a consequence of hypodopaminergic activity, individuals may present with reduced sexual drive, lack of motivation, reduced cognitive functions, and bad mood (Schlaepfer et al. 2012). Therefore, drugs that either increase the secretion of both dopamine and norepinephrine or induce these processes may show positive effects on sexual activity (Stahl 2014).

Known to have no effect on the serotonergic receptors (Croft et al. 2002), bupropion shows action on the neurotransmitters dopamine and norepinephrine (Stahl 2014). When compared to SSRI, bupropion has been less reported to be associated with sexual dysfunction. Studies have demonstrated that bupropion can reverse sexual dysfunction and have also shown that the incidence of sexual dysfunction induced by this drug is low (Kennedy et al. 2002). Furthermore, it is considered that bupropion could be effective in the treatment of sexual dysfunction resulting from the use of SSRI and SNRI (Clayton et al. 2014). The effect of bupropion on sexual dysfunction has been previously demonstrated in human studies. Bupropion has been shown to be more effective than placebo in reversing sexual dysfunction caused by SSRI therapy. However, sexual dysfunction was measured by questionnaire/scale in this study (Safarinejad 2010).

Produced in the hypothalamus, gonadotropin-releasing hormone (GnRH) induces the release of the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the hypophysis. FSH initiates spermatogenesis through its effects on the Sertoli cells. On the other hand, LH induces the production of testosterone in the Leydig cells (Corradi et al. 2016). Testosterone, secreted as a result of the activation of the hypothalamus-hypophysis-gonadal axis, is the main hormone involved in the regulation of the male libido and male stimulation (Corona et al. 2016). Testosterone deficiency has been reported to be associated with reduced libido and erectile dysfunction (Morgentaler et al. 2016). Prolactin may affect spermatogenesis by inhibiting the release of GnRH or by binding to the receptors on the Leydig and Sertoli cells (Dabbous and Atkin 2018). It is stated that hyperprolactinemia in male individuals is associated with various conditions such as decreased erectile dysfunction, gynecomastia, and infertility (Buvat 2003).

In view of this data, the present study was aimed at the determination of testosterone, LH, FSH, and prolactin levels before and after bupropion treatment and pre- and post-treatment libido scores. To the authors' knowledge, there is no previous study on the effects of bupropion on gonadal hormones in dogs. Although very few studies have been published on the effects of bupropion on gonads in mice (Cavariani et al. 2015; Yardimci et al. 2019; Ulker et al. 2020), prolactin levels were not measured in these studies. Prolactin stimulates LH in the Leydig cells of the testes, increasing testosterone production (Jöchle 1997). Prolactin plays a role in controlling male copulatory behavior in humans, mice, rats, and other rodents (Ata Sedik et al. 2022). The measurement of prolactin levels alongside testosterone, LH, and FSH levels, and the evaluation of these levels together with libido scores in the present study are expected to contribute to the scientific literature with more substantial data. In addition, since the evaluation of libido levels in dogs will be presented

based on more objective evidence, we aimed to conduct this study on dogs.

Materials and methods

Study animals

The animals were selected among male dogs, which were admitted to the Animal Hospital of Harran University, Faculty of Veterinary Medicine, with the complaint of sexual disinterest. The study animals comprised ten 2-year-old male dogs. All animals underwent comprehensive clinical evaluation (body condition score, vital signs, genital discharge, examination of peripheral lymph nodes, evaluation of pain detection in abdominal palpation). Additionally, a complete physical evaluation of the genital area (medical history, visual assessment of the scrotum, palpation of the testicles, examination of the penis and prepuce), routine blood values, and ultrasonographic examination of the genital organs was performed. Animals that did not show any clinical abnormalities were used in the study. Among the animals brought to the clinic, those with very weak libido were included in the study.

All animals were scored for libido behavior before the study, and blood samples were taken. Libido behavior scoring was observed by the male dog's exposing to a female dog in estrus. All dogs had no previous experience with semen collection by digital manipulation; therefore, libido subjective score was not biased by a reproductive conditioning. Prior to treatment, the animals underwent libido scoring and blood sampling. Libido scoring based on reaction time was adapted from the study by Kumar et al. (2008). Libido scoring was based on the reaction time of the dogs during the collection of semen samples. The libido of the dogs was scored as follows: very weak libido (reaction time > 15 min), weak libido (5 min < reaction time < 15 min), and good libido (reaction time < 5 min). As a result, male dogs, which had a weak libido, showed no interest in bitches and displayed no copulation behavior, were included in this study (Kumar et al. 2008).

Bupropion treatment

The bupropion dose administered to the animals in the present study was selected based on the doses used in a previous study aimed at the investigation of the hemodynamic effects of bupropion in dogs (Cicardo et al. 1986). The animals were weighed at the beginning of the study, and the administration doses were adjusted according to their body weights. Each dog was administered bupropion at a daily dose of 3 mg/kg.bw by oral route for a period of 3 days, 1 h before semen collection. Libido scoring was performed before and after bupropion treatment. All animals were subjected to standard feeding throughout the study period. Neither food nor water was restricted. No sign of general toxicity, such as piloerection, weight loss, and decrease in food and water intake, was observed in any of the animals throughout the study.

Hormone analyses

Blood samples were taken from each animal included in the study, before treatment (day 0) and after treatment, early in the morning at the same time point (08.00 am). Blood samples were collected once weekly for a period of 4 weeks, 1 h after the administration of bupropion. All blood samples were centrifuged at 1500 g for 10 min for the extraction of the serum, and the resulting sera were stored at − 20 °C until being used for analysis.

Assays were performed using Bioassay Technology Laboratory's (*BT LAB*) Canine competitive Enzyme Linked Immunosorbent Assay (ELISA) kits according to the manufacturer's instructions. Catalog and lot numbers of commercial kits used in hormone analysis are as follows: serum testosterone (*BT LAB*, Cat no: EA0006Ca; Lot: 202,308,018, Shanghai, China), serum LH (*BT LAB*, Cat no: EA0011Ca; Lot: 202,308,018, Shanghai, China), serum FSH (*BT LAB*, Cat no: EA0014Ca; Lot: 202,308,018, Shanghai, China), and serum prolactin (*BT LAB*, Cat no: EA000Ca; Lot: 202,308,018, Shanghai, China) levels. Testosterone ng/mL, LH, and FSH levels were reported in mIU/mL, while prolactin levels were expressed in uIU/mL.

Statistical analyses

The study data were analyzed with the "IBM SPSS Statistics 26" package program. Prior to data analysis, the parameters were evaluated for normal distribution with the *Shapiro–Wilk* test. Data were expressed as mean ± standard deviation. Friedman analysis was used to evaluate repeated measurements. The reason for the difference between the groups was determined with Wilcoxon's signed rank test. The new level of statistical significance was set with the Bonferroni correction. The statistical significance of the tests was set at a level of $p < 0.05$.

Results

Testosterone levels were calculated as 1.72 ± 0.98 ng/mL on average before bupropion treatment, 1.73 ± 0.95 ng/mL on average after 1 week of treatment, 1.78 ± 0.96 ng/mL on average after 2 weeks of treatment, 1.70 ± 0.96 ng/mL on average after 3 weeks of treatment, and 1.74 ± 0.93 ng/mL on average after 4 weeks of treatment. Friedman test results

showed that there was no statistically significant difference between the study groups (x^2: 2.566; $p > 0.05$).

The mean LH levels determined in the study were 1.14 ± 0.81 mIU/mL before bupropion treatment, 1.58 ± 0.93 mIU/mL 1 week after the treatment, 1.69 ± 0.87 mIU/mL 2 weeks after the treatment, 1.93 ± 0.67 mIU/mL 3 weeks after the treatment, and 1.69 ± 0.84 mIU/mL 4 weeks after the treatment, and the Friedman test showed that the groups significantly differed from each other for these levels (x^2: 22.653; $p < 0.001$). Wilcoxon's signed rank test revealed that the LH levels of the dogs during the first 4 weeks after bupropion treatment were higher than the levels measured before the treatment. According to this finding, LH levels in the 1 st, 2nd, 3rd, and 4th weeks after treatment are not different from each other. However, LH levels in all weeks after treatment are significantly higher than before treatment.

The mean FSH levels measured in the present study were 3.86 ± 1.21 mIU/mL before bupropion treatment, 3.66 ± 1.07 mIU/mL 1 week after the treatment, 3.67 ± 1.06 mIU/mL 2 weeks after the treatment, 3.74 ± 1.07 mIU/mL 3 weeks after the treatment, and 3.70 ± 1.18 mIU/mL 4 weeks after the treatment, and based on analysis, it was ascertained that there was no statistically significant difference between the study groups (x^2: 7.095; $p > 0.05$).

The mean prolactin levels measured in this study were 171.03 ± 73.66 ulU/mL before bupropion treatment, 167.76 ± 69.14 ulU/mL 1 week after the treatment, 169.02 ± 71.23 ulU/mL 2 weeks after the treatment, 170.84 ± 72.61 ulU/mL 3 weeks after the treatment, and 171.59 ± 73.94 ulU/mL 4 weeks after the treatment, and analysis showed that there was no statistically significant difference between the study groups (x^2: 5.192; $p > 0.05$).

According to these findings, it was determined that serum testosterone, FSH, and prolactin levels were not statistically affected by bupropion treatment in dogs (Figs. 1, 2 and 3). On the other hand, Wilcoxon's signed rank test demonstrated that the LH levels measured during the first 4 weeks after bupropion treatment were higher than the levels measured before the treatment (Fig. 4). Moreover, the results of the libido scoring of the dogs performed before and after bupropion treatment were observed to be similar (Table 1).

Discussion

The present study was aimed at the investigation of potential changes in the libido scores together with the pre-treatment and post-treatment serum testosterone, LH, FSH, and prolactin levels of male dogs, which had a weak libido and were treated for 3 days with 3 mg/kg.bw of bupropion. Post-treatment measurements were performed for a period of 4 weeks after the administration of bupropion. Based on the findings of this study, there was no statistically significant difference between the serum testosterone, FSH, and prolactin levels measured before bupropion treatment and during the 4-week period after treatment ($p > 0.05$). On the other hand, the LH levels measured throughout the first 4 weeks after treatment were found to be significantly higher than the levels measured before treatment ($p < 0.05$). In a study in rats by Cavariani and colleagues, LH levels increased and epididymal duct contractility increased after treatment with 15 mg/kg bupropion. But sperm quality was not affected. Furthermore, no change was determined in the serum testosterone and FSH levels of the groups treated with 15 mg/kg and 30 mg/kg of bupropion. Moreover, sperm quality was reported to have decreased in the rats treated with 30 mg/kg of bupropion. The sexual behavior of the male rats was observed not to have changed with bupropion treatment at both administration doses (Cavariani et al. 2015). High testosterone is a negative feedback signal for the hypothalamus-hypophysis-gonadal axis and inhibits the secretion of both GnRH and LH. Thus, low testosterone levels could result

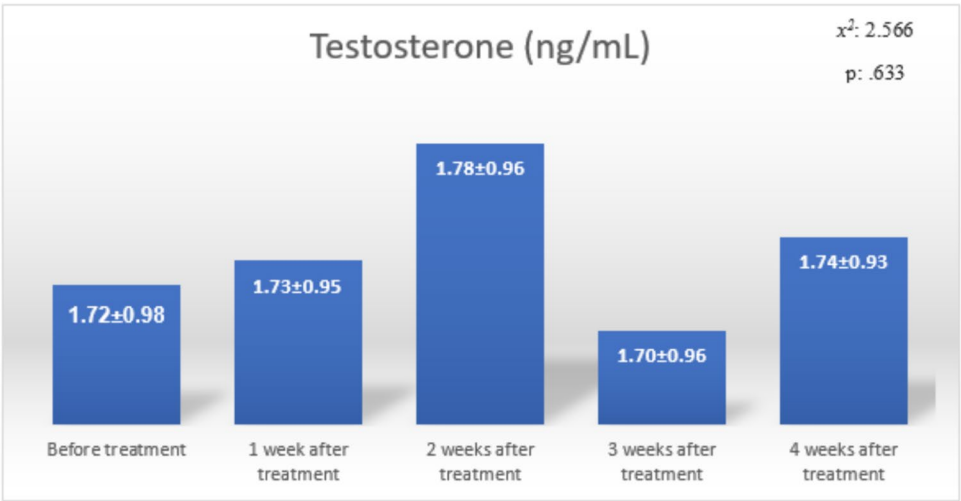

Fig. 1 The comparison of testosterone levels between the period before bupropion treatment and the 4-week period after bupropion treatment ($n = 10$)

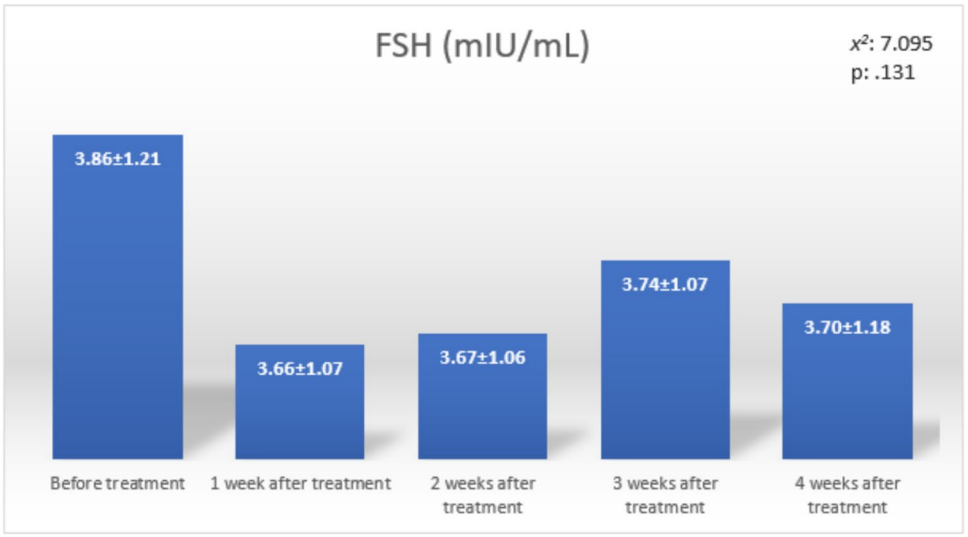

Fig. 2 The comparison of FSH levels between the period before bupropion treatment and the 4-week period after bupropion treatment ($n = 10$)

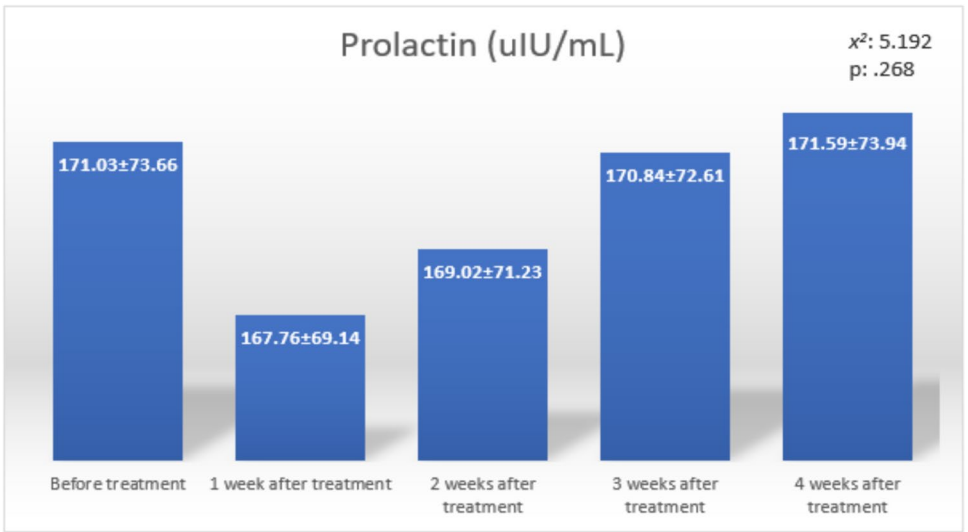

Fig. 3 The comparison of prolactin levels between the period before bupropion treatment and the 4-week period after bupropion treatment ($n = 10$)

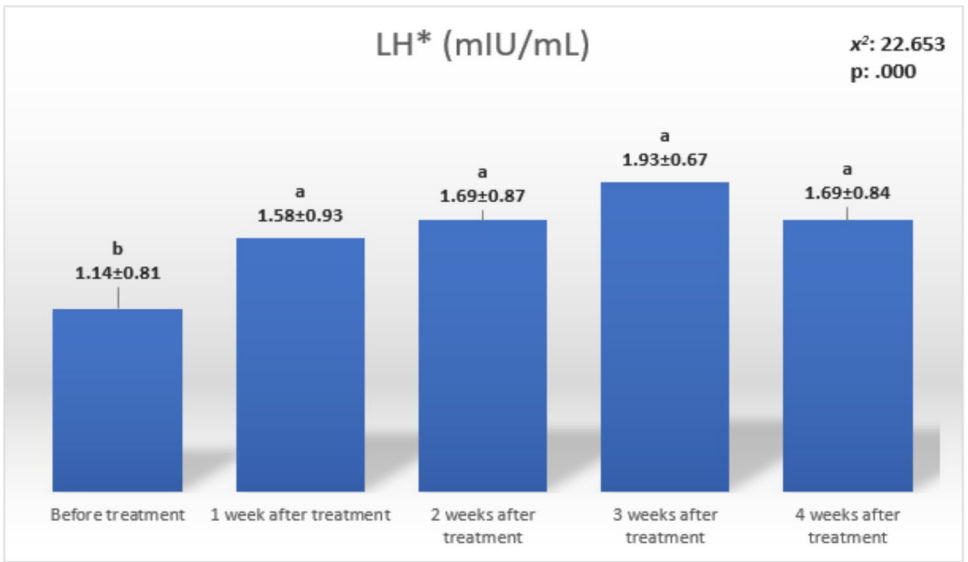

Fig. 4 The comparison of LH levels between the period before bupropion treatment and the 4-week period after bupropion treatment ($n = 10$). a > b; *the Bonferroni correction was made ($p < 0.01$ was considered statistically significant)

Table 1 Libido scores before and after bupropion treatment

Libido score	Before treatment		After treatment	
	n	%	n	%
Very weak libido	10	100	10	100
Weak libido	0	0	0	0
Good libido	0	0	0	0

in increased LH secretion (Roelfsema and Veldhuis 2016). There are very few literature reports available on the effects of burproprion on gonadal hormones, and these reports point out different results. In a study by Yardimci et al. (2019), the LH and testosterone levels of rats treated with 17 mg/kg of bupropion were determined to be significantly higher than those of the control subjects, whereas no difference was reported between the FSH levels of these two groups. In a study by Ulker et al. (2020), female rats administered 17 mg/kg of bupropion were determined to display decreased LH levels after treatment, yet no statistically significant change was detected in the FSH and estradiol levels of the treated animals. This was attributed to estradiol levels, increased by bupropion treatment, having decreased LH secretion by the hypophysis (Ulker et al. 2020).

There are various literature reports suggesting both positive and negative effects for bupropion in the treatment of sexual dysfunction. In a previous study, based on the use of the International Index of Erectile Function (IIEF) IIEF-5 survey for evaluating the treatment of sexual dysfunction in men with chronic kidney disease, the administration of bupropion at a dose of 100 mg/kg for 10 weeks was determined to be both effective and safe (Ghoreishi et al. 2019). In another study on the treatment of methadone-induced sexual dysfunction with the administration of 200 mg/kg of bupropion for 8 weeks, evaluation with the Arizona Sexual Experience Scale (ASEX) survey proved this agent to be effective (Salehi et al. 2015). On the other hand, the investigation of the development of the progeny resulting from the mating of female mice with male mice, which were administered 40 mg/kg of bupropion, revealed bupropion treatment to have decreased testosterone and sperm production and to have shown toxic effects on the testicular function of the progeny alongside potential teratogenic effects (Sanches et al. 2018). In an observational study on the intraperitoneal administration of 5 mg/kg bupropion to female mice for 14 days, this treatment was determined to have induced the mating behavior of the animals (Ventura-Aquino and Fernández-Guasti 2013). Low testosterone levels may arise from testicular dysfunction, anomalies of the hypophysis and/or the hypothalamus, which affect hormone secretion, as well as from the use of certain pharmaceuticals (Traish 2018). Testosterone levels below the normal values have been reported to be associated with loss of vitality, motivation, muscle mass, libido, and bone tissue (Morgentaler et al. 2016) and have also been indicated to cause several problems including erectile dysfunction, decrease of spontaneous erection, and late ejaculation (Kandeel et al. 2001). In the present study, the libido of the dogs having not shown any change after bupropion treatment was attributed to the testosterone levels having not increased. This demonstrates the specific role that testosterone plays in the libido (Corona et al. 2022). In a study on middle-aged and elderly men, the daily transdermal administration of dihydrotestosterone, which is the active form of testosterone, at a dose of 70 mg for 24 months resulted in a decrease in the sexual desire of the patients (Sartorius et al. 2014). To date, in the majority of studies, the effects of bupropion on sexual desire and dysfunction have been assessed generally by the subjective self-assessment of individuals rather than by objective measurements (Safarinejad 2010; Aydogan et al. 2023). In a study on men who received SSRI treatment and had a low libido, sexual function was evaluated using the Clinical Global Impression-Sexual Function (CGI-SF) and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) tools after the administration of bupropion at a daily dose of 300 mg for 12 weeks. Based on evaluation, it was determined that bupropion was more effective than placebo treatment in reversing the sexual dysfunction caused by SSRI treatment (Safarinejad 2010). In another study aimed at determining the consistency of testosterone treatment with the sexual dysfunction evaluation scales ASEX and IIEF, men aged 18–30 years were given testosterone replacement treatment for 3 weeks. After treatment, it was determined that while the FSH and LH levels of the patients had not changed, their total testosterone levels had significantly increased. All three of the ASEX, IIEF-5, and IIEF-15 scales used in the study gave results, which were in agreement with the change in the testosterone levels of the patients. It was underlined that the measurement tools used in the study were functional scales used to evaluate sexual function in hypogonadotropic hypogonadism patients (Aydogan et al. 2023). Although several other studies have claimed a statistically significant correlation between testosterone deficiency and sexual dysfunction (Corona et al. 2021; Barbonetti et al. 2021), the specificity of this claim is weak and there is a need for further research to obtain more solid data on sexual desire and function. Multiple determinants, including, among others, depression, anxiety, attraction, sexual function, cultural factors, sex roles, communication, and conflict, may cause symptoms of sexual incompetence (Nimbi et al. 2020).

In the present study, we also determined that no statistically significant change had occurred in the serum prolactin levels of the animals after bupropion treatment. In a previous study by Whiteman et al. (1982), based on comparison with placebo treatment, it was demonstrated that, when administered at doses up to 100 mg, bupropion did not affect plasma

prolactin levels (Whiteman et al. 1982). On the other hand, in a study by Susan Smith and Bartke (1987), the serum LH levels of rats with induced hyperprolactinemia were found to be lower than the levels of the control subjects. This result was interpreted as an indication of prolactin having the potential to cause erectile dysfunction through its inhibitory effect on LH (Smith and Bartke 1987). In our study, we determined that while there was no change in the serum prolactin levels, the LH levels had increased. In the present study, in the dogs treated with bupropion for a low libido, no statistically significant change was determined in the post-treatment libido scores and prolactin levels. In a review by Chanson (2022), it was indicated that, while the prevalence of hyperprolactinemia was reported to be very low in the majority of patients treated with antidepressants, the prevalence of hyperprolactinemia was reported to be higher in patients treated with antipsychotics, which show effect by either blocking or lessening dopamine activity at the level of the dopamine type-2 receptors of the mesolimbic, nigrostriatal, and tuberoinfundibular pathways (Chanson 2022). It has been reported that bupropion, as a dopamine reuptake inhibitor, increases endogenous dopamine levels and facilitates erection (Adachi et al. 2003). It is considered that dopamine shows facilitatory effects on sexual motivation, copulation competence, and genital reflexes. Dopamine is considered to regulate genital reflexes, mating, and particularly sexual motivation in the medial preoptic area (Hull et al. 2004).

The inhibitory effect of dopamine on prolactin secretion is mediated by the tuberoinfundibular dopaminergic and tuberohypophysial dopaminergic neurons (Ben-Jonathan and Hnasko 2001). In males, hyperprolactinemia has been indicated to be associated with a decrease in erectile dysfunction, gynecomastia, and infertility (Buvat 2003). While it has been claimed that long-term hyperprolactinemia could be associated with sexual dysfunction (Badal et al. 2015), it has also been reported that the percentage of hyperprolactinemia among individuals with erectile dysfunction was only 2% (Johnson and Jarow 1992). High prolactin levels may cause the downregulation of dopamine receptors localized to the hypothalamic regions related to sexual and erectile function (Badal et al. 2015).

Conclusion

No change having been observed in the libido scores, despite the LH levels having increased after bupropion treatment, was attributed to the testosterone levels having not increased. Testosterone, known to affect sexual function and libido, did not cause any significant change in the sexual activity of dogs after bupropion treatment. However, it is still not known whether the improving effect of bupropion on sexual function is related to testosterone or dopamine. As a result, given that hormone-receptor interactions and several hormones, neurotransmitters, and peptides are responsible for the regulation of sexual functions, research on the hormonal background of bupropion-induced changes in sexual function and libido should not overlook the investigation of dopamine and its receptors. While many surveys have reported positive effects of bupropion on sexual function and libido, the results of these surveys are based on the subjective evaluations of individuals. To determine the exact effects of bupropion, there is a need for further research based on the objective evaluation of libido, spermatological parameters, and sexual function. One of the limitations of this study was the prolactin levels of the dogs with a weak libido having not been compared to those of dogs with a normal or high libido. Another limitation was bupropion having been administered for a period of 3 days and at low doses. We consider that a better understanding of the effects of bupropion in the treatment of sexual function can be obtained by the use of bupropion at varying doses for longer periods in double-blind studies performed on a larger number of randomized and controlled subjects and by the comparison of bupropion treatment with other treatment methods.

Author contributions Ç.Ç., Z.G. M.C. and E.G. selection of the experimental animals, libido scoring, sample collection for use in analyses. A.K. and N.Y. biochemical analyses. N.Y. statistical analyses. Ç.Ç., Z.G., E.G., A.K., and N.Y. manuscript writing. All authors reviewed the results and approved the final version of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Compliance with ethical standards

Funding This study received financial support from the Scientific Research Projects Unit of Harran University (Project Number: 22297).

Conflict of interest The authors declare no competing interests.

Ethical approval This study was conducted pursuant to the ethical permission dated November 8, 2022 and numbered 179895, granted by the Local Ethics Board for Animal Experiments of Harran University.

Informed consent For this type of study, informed consent is not required.

Consent for publication For this type of study, consent for publication is not required.

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