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# Comparative evaluation of cyproheptadine and mirtazapine in enhancing post-surgical appetite in rabbits following ovariohysterectomy

Parham Rahmanian [1], Mohammad Arad Zandieh [2], Alireza Jahandideh [3], Ahmad Asghari * [3]

[1] *Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[2] *Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran*
[3] *Department of Clinical Science, Science and Research Branch, Islamic Azad University, Tehran, Iran*

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* *Corresponding author:*
*Ahmad Asghari*
*Email: m.a.mdphd90@gmail.com*

***Reviewed by:***
*Erfan Hamedi*
*Department of Clinical Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran*

**Abstract**

Ovariohysterectomy (OHE) is a fundamental surgical procedure for companion animal population control and the prevention of life-threatening reproductive diseases, significantly improving animal welfare. Despite its routine nature, post-operative anorexia is a common complication that can impede recovery, prolong convalescence, and negatively impact overall health outcomes. This study aimed to rigorously evaluate and compare the efficacy of two widely used appetite stimulants, cyproheptadine and mirtazapine, in enhancing feed intake of healthy female rabbits during the critical post-OHE period. Sixty healthy rabbits were randomly assigned to one of three oral treatment groups following surgery: cyproheptadine (5 mg/kg), mirtazapine (1.88 mg/kg), and a placebo. Feed consumption was meticulously monitored and statistically analyzed. The results compellingly demonstrated that cyproheptadine administration led to a statistically significant increase in cumulative feed consumption when compared to the placebo group ($p = 0.017$). Although the difference in feed intake between the cyproheptadine and mirtazapine groups did not achieve statistical significance ($p = 0.056$), cyproheptadine consistently exhibited a more pronounced and potent appetite-stimulating effect. Mirtazapine demonstrated a moderate ability to increase feed intake. Crucially, both medications were well tolerated by the rabbits, with no adverse effects noted, confirming their safety profiles for short-term post-operative application. Cyproheptadine was thus identified as the more effective appetite stimulant in this post-surgical rabbit model, a finding that aligns with its known antihistaminic and serotonin-antagonistic pharmacological mechanisms. While these findings are promising for managing post-OHE anorexia, further research is essential. Broader applications of these drugs in veterinary medicine to improve post-surgical well-being are warranted.



## 1. Introduction

Globally, controlling the population of pets and stray animals is an ongoing priority for various practical and ethical reasons. To this end, strategies are typically divided into two main categories: surgical approaches, such as sterilization, and nonsurgical approaches, which include immunological, hormonal, or mechanical interventions, such as the use of intrauterine devices. Among these, ovariohysterectomy (OHE), commonly referred to as spaying, remains one of the most effective and frequently performed surgical procedures for female pets. This surgery involves the removal of the ovaries and uterus and is carried out under general anesthesia, with the ideal timing being before the animal reaches sexual maturity. Recovery generally occurs within 5 to 7 days (DeTora and McCarthy 2011; Kustritz 2018). This procedure is widely acknowledged for its advantages, particularly its ability to prevent unintended pregnancies. By removing the reproductive organs, the animal is rendered infertile, which is particularly beneficial in areas where excessive stray animal populations, such as feral dogs, pose significant challenges to public health and ecological stability (Marvel 2022). Sterilization not only reduces overpopulation and its associated problems but also alleviates pressure on limited resources in animal shelters, enabling more effective care for the animals housed there (Kreisler et al. 2018). In addition to population control, OHE offers significant health benefits. The procedure is linked to a marked reduction in the risk of serious reproductive health conditions such as pyometra, uterine neoplasms, ovarian or vaginal tumors, uterine cysts, torsion, prolapse, and infections. It also helps decrease the likelihood of mammary tumors, a common cause of mortality in female dogs. Spaying has further been shown to manage hormonal disorders, diabetes, and epilepsy in certain cases. Collectively, these benefits extend both the lifespan and the quality of life of companion animals (Van Goethem et al. 2006).

Neutering of female rabbits (*Oryctolagus cuniculus*) is primarily done to avoid unintended reproduction. Uterine adenocarcinoma is the most prevalent tumor in female rabbits, with a significant risk if they remain unspayed. Consequently, OHE is advised for all pet rabbits that are not intended for breeding. Although uterine neoplasia is often asymptomatic, it may lead to issues such as reproductive failure, vaginal bleeding, and persistent weight loss. However, when identified before metastasis, OHE is the treatment of choice (Tonks and Atlas 2007; Isaza and Isaza 2020). In addition, this intervention can help

prevent or address various uterine disorders, such as endometritis, endometrial hyperplasia, pyometra, hydrometra, and uterine aneurysms. Research has extensively examined the prevalence and types of uterine conditions in rabbits and endometrial hyperplasia was most frequently observed (in nearly 30% of cases), followed by uterine adenocarcinoma (21%), and tumorous lesions were seen in half of the cases (Saito et al. 2002; Walter et al. 2010). Additionally, unspayed female rabbits are prone to pseudo-pregnancy, where hormonal changes mimic actual pregnancy, leading to problematic behaviors like aggression, fur plucking, and territorial urine spraying. Performing OHE in advance can mitigate these issues. While the advantages of OHE are well-recognized, there is limited research on the potential long-term biological consequences of these procedures (Isaza and Isaza 2020; Vicente-Carrillo et al. 2025).

OHE, while generally safe due to advancements in veterinary medicine, carries potential risks and drawbacks inherent to any surgical procedure. These include the possibility of infection, bleeding, inflammatory reactions like peritonitis, incision site hernia, prolonged recovery, granulomas affecting reproductive organs, urinary incontinence, adhesions, and anesthetic complications. Although studies indicate that complications can occur, their incidence is typically lower when the surgery is performed by a proficient and experienced veterinarian (Gadelha et al. 2004; Buote 2015). Surgical removal of the ovaries can lead to hormonal imbalances by halting the natural production of vital reproductive hormones like estrogen and progesterone. This disruption may affect the animal's metabolism, cause behavioral shifts, and result in decreased appetite, especially when combined with anesthetic drugs (Adin 2011).

Following surgery, appetite loss in pets has been a concern, leading to the investigation of medications like mirtazapine and cyproheptadine as potential treatments (Ozawa et al. 2022). Originally intended as a human antidepressant, mirtazapine has been found to effectively stimulate appetite in pets by acting on brain serotonin receptors. Its mechanism of action involves blocking these receptors, resulting in increased appetite and decreased nausea. This generally well-tolerated medication with few side effects in veterinary applications is particularly beneficial for short-term appetite enhancement following surgical procedures (Weeth 2015; Gray et al. 2018). On the other hand, cyproheptadine, an antihistamine, significantly stimulates appetite by blocking histamine receptors in the brain. This action helps reduce nausea and promote feed consumption. Nevertheless, its use can lead to side effects such as drowsiness, dry mouth, and, infrequently, urinary retention (Harrison et al. 2019). Thus, this study sought to assess and compare the efficacy of mirtazapine and cyproheptadine in stimulating appetite and enhancing feed consumption in healthy rabbits following OHE.

## 2. Materials and methods

### 2.1. Study population and housing conditions

Sixty healthy female rabbits, aged 3-4 months and sourced from the Iran Pasteur Institute, were used in this study. Throughout the investigation, the rabbits were maintained in ideal environmental conditions and had unrestricted access to both fresh water and a nutritionally complete diet, in accordance with rabbit welfare standards (Trocino and Xiccato 2006). Prior to their inclusion in the study, the general health of all rabbits was verified through the clinical and paraclinical assessment of baseline physiological parameters, including body temperature, respiration rate, and heart rate.

### 2.2 Surgical Procedure

Anesthetized using a combination of xylazine (5 mg/kg) and ketamine (35 mg/kg), all the rabbits underwent OHE. The surgical area, from the xiphoid process to the pelvic region, was shaved, cleansed, and prepared under sterile surgical conditions. A 4–8 cm incision was made in the mid-ventral abdominal wall, exposing the linea alba, which was carefully elevated and incised to access the ovaries and uterine horns (Fig. 1). These structures were separated from the surrounding tissue, ligated using absorbable sutures, and removed (Fig. 2). Post-procedure, the abdominal wall was closed layer by layer (muscle, fascia, and skin) to ensure proper healing and minimize any post-surgical complications, such as herniation or infection (Richardson and Flecknell 2006).

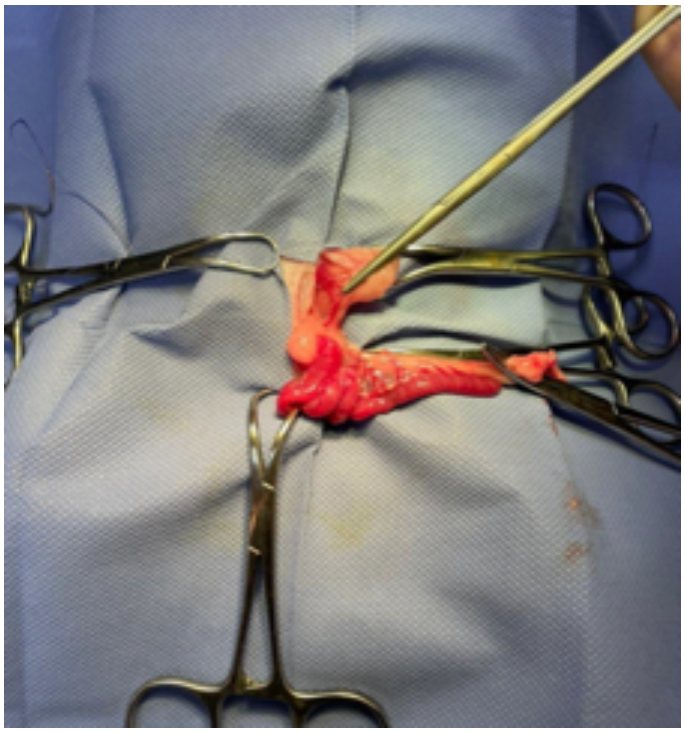

***Fig. 1.*** *OHE surgery in a rabbit*

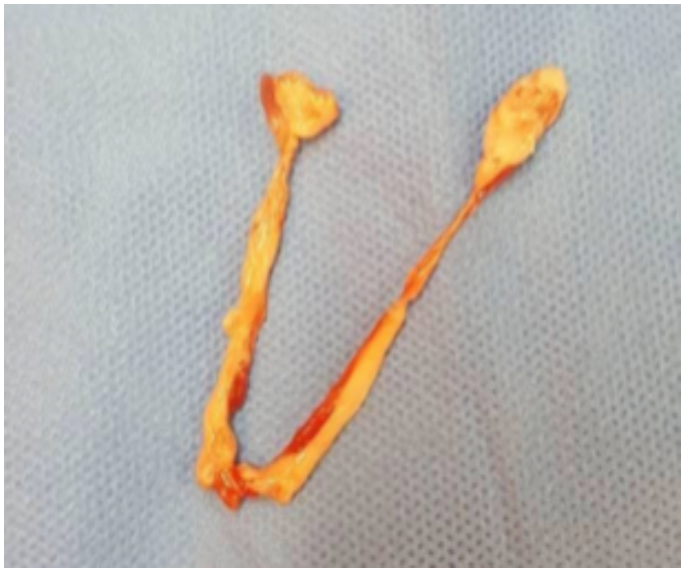

***Fig. 2.*** *Ovary and uterus removed using the ovariohysterectomy method*

### 2.3. Drug Preparation and Experimental Groups

Rabbits in three experimental groups were studied, with age and body weight (average 4 months and 2 kg, respectively) controlled for uniformity. Cyproheptadine (100 mg capsules in 5 mL distilled water) and mirtazapine (15 mg tablets in 2 mL distilled water) were prepared. Dosages were calculated to be 5 mg/kg for cyproheptadine and 1.88 mg/kg for mirtazapine. A placebo solution of equal volume, containing only distilled water, was also prepared (Fig. 3). Following surgical recovery, the rabbits were divided into three groups (n = 20 each): Group 1 received 0.5 mL of cyproheptadine solution orally, Group 2 received 0.5 mL of mirtazapine solution orally, and Group 3 received 0.5 mL of placebo solution orally.

***Fig. 3.*** *Administration of drugs to rabbits*

### 2.4. Statistical Analysis

All statistical analyses were conducted using SPSS software. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test, while Bartlett's test verified homogeneity of variance. A one-way ANOVA was employed to evaluate differences across the experimental groups.

## 3. Results and Discussion

The results of this study highlighted a significant difference in feed consumption between Group 1 (cyproheptadine) and Group 3 (placebo) ($P = 0.017$). However, no significant difference was observed between Group 1 (cyproheptadine) and Group 2 (mirtazapine) ($P > 0.05$). Similarly, there was no significant difference between Group 2 (mirtazapine) and Group 3 (placebo) ($P > 0.05$). This study compared the cumulative feed intake (g) of three groups over an 8-hour period, and significant differences were observed (Fig. 4). Group 1, receiving 0.5 mL of oral cyproheptadine, consistently displayed the highest feed consumption, reaching the greatest overall intake by the study's conclusion. Group 2, administered 0.5 mL of oral mirtazapine, showed a moderate level of feed consumption, consistently ranking between Group 1 and Group 3 (placebo). The placebo group exhibited the lowest feed intake throughout the study. Fig. 4 visually represents these trends, showing cumulative feed intake at 2, 4, 6, and 8 hours post-administration, with error bars representing +/- 2 standard deviations (SD) to illustrate within-group variability.

Certain medications can affect appetite by either stimulating or suppressing brain centers, leading to therapeutic benefits or unwanted side effects. Drugs can also influence nausea and vomiting or alter taste, thereby impacting feed intake. Post-operative patients commonly face issues like nausea, vomiting, fever, and appetite loss, hindering proper nutrition (O'farrell and Peachey 1990). Consequently, there is growing research interest in strategies to enhance feed intake following procedures such as OHE (Fantinati et al. 2020). In the present study, cyproheptadine significantly increased feed intake in rabbits compared to placebo, likely due to its antihistamine and serotonin-antagonizing effects, particularly 5-HT2 receptor blockade in the hypothalamus. While mirtazapine also showed a stimulatory effect, it was not statistically significant, indicating a weaker impact than cyproheptadine. These results suggest that cyproheptadine is a more potent appetite stimulant in rabbits, while mirtazapine's effect is less pronounced. According to Bertrand et al. (2021), cyproheptadine is considered a safe drug. They noted that while mild neurological side effects are relatively common, liver toxicity is rare. The drug's ability to stimulate appetite has been well-documented (Bertrand et al. 2021). Cyproheptadine, a first-generation H1 antihistamine, was first introduced in the 1960s to treat allergies and itching caused by skin conditions. However, its appetite-stimulating side effect soon became a point of interest (Couluris et al. 2008). Today, cyproheptadine is approved in the United States for stimulating appetite in adults and children over two years old. It has also been studied for gastrointestinal disorders and migraine prevention (Okuma et al. 2013; Madani et al. 2016). Consistent with previous research, the findings of this study confirm that cyproheptadine had the most significant appetite-stimulating effect.

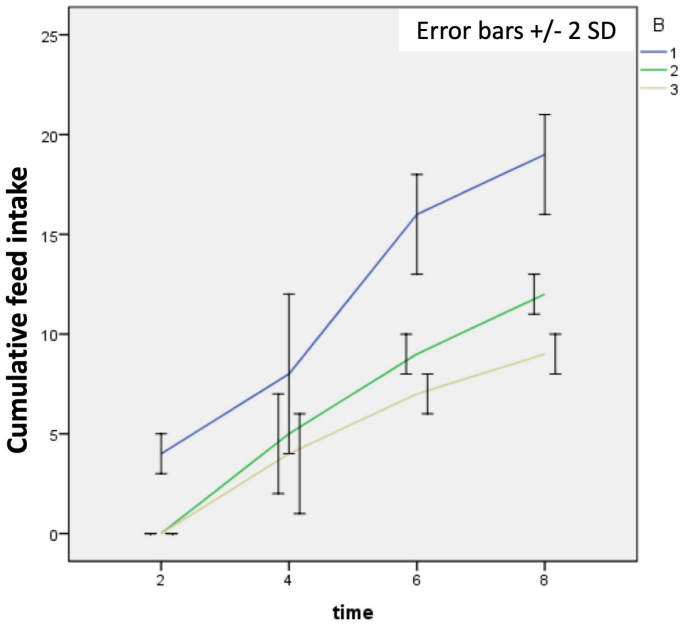


***Fig. 4.*** *Comparison of cumulative feed intake (g) among the studied groups at 2, 4, 6, and 8 hours post-administration. Group 1 (blue line) received cyproheptadine, Group 2 (green line) received mirtazapine, and Group 3 (beige line) received a placebo. Error bars represent +/- 2 SD*

Harrison et al. (2019) conducted a systematic review of cyproheptadine and concluded that it is a safe and well-tolerated drug that effectively aids weight gain in underweight individuals. Although the drug is generally considered safe, rare cases of hepatotoxicity warrant monitoring (Bertrand et al. 2021). Overdoses have been associated with anticholinergic syndrome, seizures, psychosis, and

cardiorespiratory arrest (Chertoff et al. 2014). While cyproheptadine is now primarily used for its appetite-stimulating effects, newer alternatives have largely replaced its use for allergy treatment (Rodriguez et al. 2013). Although generally safe, cyproheptadine should not be used in patients with preexisting liver conditions, and future studies should closely monitor its potential liver-related side effects. Kazemi et al. (2017) evaluated the effects of cyproheptadine hydrochloride on weight gain in underweight children with anorexia. They found that children treated with cyproheptadine gained significantly more weight compared to those in the placebo group. Additionally, anorexia symptoms resolved in 100% of the cyproheptadine group compared to 52.7% of the placebo group, a statistically significant difference ($P = 0.005$). No adverse effects were reported by them. These findings align with the current study, which also demonstrated that cyproheptadine significantly increased appetite.

Mirtazapine, a serotoninergic antidepressant, is another drug with appetite-stimulating properties. It is often prescribed for sleep disorders (Delaney 2006). It works by blocking alpha-2 adrenergic receptors and 5-HT2A and 5-HT2C serotonin receptors, which helps improve mood and behavior (Quimby and Lunn 2013; Harris et al. 2017). Approved by the U.S. FDA in 1996, mirtazapine is primarily used to treat depression but is also effective as an anti-anxiety, sleep-inducing, anti-nausea, and appetite-stimulating drug (Wong and Pinkney 2004). In this study, mirtazapine was shown to increase appetite and feed intake, though its effect was less pronounced than cyproheptadine. Mirtazapine is quickly absorbed in the gastrointestinal tract, reaching peak blood levels within two hours. It is extensively metabolized in the liver through demethylation and oxidation, involving cytochrome P450 enzymes. Its active metabolite is excreted primarily in urine (75%) and feces (15%), with a plasma half-life ranging from 20 to 40 hours. Animal studies have shown that it crosses the placenta and is distributed in breast milk (Woods and D'Alessio 2008; Brunetto et al. 2010; Johnson and Freeman 2017).

Fantinati et al. (2020) compared gabapentin and mirtazapine for their appetite-stimulating effects in healthy cats after ovariohysterectomy. Both drugs significantly increased feed intake compared to the placebo, with no significant differences between the two treatments. This finding aligns with the present study. Similarly, Quimby et al. (2011) found that mirtazapine improved appetite, weight, and feed intake in cats with chronic kidney disease. In a later study, Quimby and Lunn (2013) confirmed that mirtazapine had appetite-stimulating and antiemetic effects, improving appetite and reducing vomiting in cats with chronic kidney disease.

While using cyproheptadine or mirtazapine for appetite stimulation, one has to be aware of drug-feed and drug-drug interactions. Cyproheptadine can be given with or without feed, although giving it with feed may reduce gastrointestinal upset. While feed slightly affects mirtazapine absorption, it can be given with feed if vomiting occurs when administered on an empty stomach. Both medications may interact significantly with other drugs, so a careful review of concurrent therapies is essential. A limitation of the current study is the absence of body weight monitoring. Although feed consumption is a direct measure of appetite, correlating it with changes in body weight would provide a more comprehensive understanding of the clinical impact of these appetite stimulants on post-operative recovery. Future studies should consider incorporating routine weight measurements to better elucidate the physiological benefits of these interventions.

## 4. Conclusions

Cyproheptadine effectively stimulated appetite in rabbits recovering from OHE and demonstrated greater efficacy than mirtazapine, which had moderate effects. Mirtazapine could be considered as an alternative. Both drugs were generally safe and well-tolerated in this study. However, more research is needed to determine their long-term effects, optimal dosages, and interactions with post-surgical hormonal and metabolic changes in rabbits. Future studies should also include body weight changes and explore broader uses in veterinary medicine to improve post-operative recovery and animal well-being.

## Declarations

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