

## Effect Of Lorazepam And Chlorpromazine On Food Intake In Budgerigars (*Melopsittacus Undulatus*)

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### Abstract

*Anorexia is a nonspecific sign that has multiple etiologies. The absence of nutrition can lead to an increase risk of death. Appetite stimulant drugs can play a principle role in the control of anorexic birds. In budgerigars, lorazepam at a dosage of 1 mg/kg was shown to temporarily enhance hunger and provide a sedative effect that lasts for three hours. The low dose of lorazepam may be a better appetite stimulant, and less sedative than other doses of this drug, but currently, no information is available about it. Chlorpromazine is one of the antipsychotic drugs that can cause the weight gain in humans, and animals. So far, no information available for using the antipsychotic drugs as appetite stimulant in psittacine birds. Thirty adult Healthy budgerigars in a blinded, clinical trial, the effect intramuscular injection of chlorpromazine(0.1mg/kg)or lorazepam(0.5mg/kg,1mg /kg,2mg/kg) were compared to placebo treatment(1ml/kg).Abnormal behavior were recorded by a blinded observer to treatment. Lower dosage of lorazepam(0.5mg/kg) more increased food intake in budgerigar compare to lorazepam (1mg/kg,2mg/kg). Lorazepam(2mg/kg) has no effect increased appetite in budgerigar. Compared to the placebo and other treatment groups, the group taking chlorpromazine consumed a notably greater amount of food. The lorazepam groups showed evidence of drowsiness up to two hours after the treatment, whereas the chlorpromazine and placebo groups showed no signs of sedation.*

**Keywords:** *appetite, lorazepam, chlorpromazine, food intake, budgerigar*

### Introduction

Anorexia is a nonspecific clinical sign. It may be a normal behavior (e.g., immediately before egg laying) or the result of illness. Abnormalities affecting the gastrointestinal tract, liver, kidneys, reproductive tract, or systemic disease may cause anorexia [1] Malnutrition in seriously sick patients leads to the muscle catabolism, protein deficiency, and addition risk of sepsis and impaired metabolic function [2, 3]. In avian species, gavage feeding, is a method necessary to prepare nutrition for the anorexic birds.[4].If gavage feeding perform incorrectly, increase risk of Mechanical damage to the oropharynx ,Accidental tracheal gavage(aspiration pneumonia ), Reflux of the formula from the crop into the oral cavity[5]. additionally, feed delivered by oral gavage needs animals to be sedated or harnessed by hand, both of them may lead to stress in the animal if unaccustomed. [6]. In order to treat anorexic patients and improve their nutritional condition while also assisting in their recovery from injuries, appetite stimulation is crucial[7]. More than 40 neurotransmitters are found as regulatory food intake in mammals and birds. Serotonin, gamma-aminobutyric acid Acetylcholine, epinephrine, norepinephrine, histamine, glutamate and glycine have been recognized as mediators in

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the modulation of feeding behavior in birds[7]. [schizophrenia](#), psychosis, and [bipolar disorders](#) are among diseases that are widely treated with chlorpromazine [8]. It is used in psittacines to treat feather pecking disorder[1] Chlorpromazine inhibit serotonin 5-HT (5-HT1A , 5-HT1B , 5HT1D ,5HT1E, 5/HT2A , 5HT2C , 5HT3 , 5HT5A , 5HT6 , 5HT7) receptor[9].5-HT1A, 5-HT6 , 5- HT2C receptors blockade was noted to increase appetite and induce weight gain[10-12].Chlorpromazine is one of the antipsychotics that can cause weight gain[13]. Benzodiazepines have dose-dependent effects on humans; at low concentrations, they function as sedatives, while at intermediate dosages, they serve as anxiolytics. Furthermore, they act as hypnotics and promote sleep when taken in high dosages [14]. Some studies show that lower dose of benzodiazepines may work to mimic the effects of increased hunger[14, 15]. At this time Limited studies were conducted on the impact of drugs on increase appetite in psittacines. one study investigated the effect of midazolam on increasing appetite in budgerigars which showed that it increases appetite within the first hour, but this study did not evaluate the exceed of one hour and different dosages of the drug. Sex did not effect in the appetite modulation of midazolam in previous research [16]. Midazolam and lorazepam stimulate appetite in budgerigars over the first five hours, according to another research. There is no difference between short-acting, and long-acting benzodiazepines. still, different dosage of drugs were not determined in reducing sedative effects and increasing food consumption in budgerigars.[17]. At the moment there are no information about antipsychotic drugs as an appetite stimulant in psittacine birds. For the first time, we are investigating the effect of chlorpromazine and low dosage of lorazepam on the appetite in budgerigars.

We hypothesized that chlorpromazine would be doing as an appetite stimulant with low sedative effect in the budgerigars. a low dose of lorazepam has a better appetite stimulant, and less sedative effect than other doses of this drug.

## Material and method

Thirty adult Healthy budgerigars (*Melopsittacus undulatus*) nine to twelve months of age, without determined sex, were included. The range of body weight was (30-45) grams. All birds were weighed with an electronic scale (accuracy to the nearest 0.1 g), and then transferred individually a wire cage (38×38×28cm). The animals were fasted for 45 minutes A cover was used for each cage to prevent the grain from being thrown out. The cages were accommodated in a climate-controlled environment room at (22°-23°C), and a 12 hours of light and dark. The birds were feeding a seed blend and free drinking water. Millet grain was used a treat. A physical examination was conducted to make sure that animals were healthy. The birds were adapted for 30 days before the start of the study.

### experimental design

A research randomized (<https://www.randomizer.org/>), blinded clinical trial design was applied., the bird underwent five treatment contained:(1) lorazepam 1 mg/kg IM(2mg/1ml, chemidarou,Iran);(2) lorazepam 0/5 mg/kg IM(2mg/1ml,chemidarou,Iran)(3) lorazepam 2 mg/kg

IM(2mg/1ml,chemidarou,Iran)(4) chlorpromazine 0/1 mg/kg IM(50mg/2ml,Tehran chemie,Iran)and (5)placebo1 ml/kg IM(distilled water for injection,samen,Iran).

Lorazepam and chlorpromazine were diluted in agreement with the order of company manual a final concentration of 1mg/ml and 0.1 mg/ml respectively. The injection was done into the pectoral muscle of each bird. Millet was weighed in each cage. Each time, the same scale (accuracy to the nearest 0.01 g) was utilized. Food intake was assessed every hour for the first eight hours and subsequently every four hours in each treatment group by a person who was not aware of the therapy. During the first four hours, every half-hour, sedation behaviors of each group ,involving (head droop, hock sitting, wing droop and closed eyes) were recorded by an observer blinded to treatment

All injections were done between the hour of 9 and 10 in the morning, and the final recording took place at 10 pm

Analysis of data

For statistical analysis, IBM SPSS version 27.0.1 was used. The univariate normal distribution was checked using the Kolmogorov-Smirnov test. The Levene's test was employed to determine variance homogeneity. One-way analysis of variance (ANOVA), and post hoc Games–Howell test was used to evaluate the effect of treatment. P-value <0.05 was determined for Statistical significance

## Result

Food intake after 1 hours the injection of lorazepam (0.5mg/kg,1mg/kg,2mg/kg) or chlorpromazine was  $4.11 \pm 1.05$ , and  $3.44 \pm 1.60$  g/kg and  $2.23 \pm 3.64$  g/kg and  $4.61 \pm 2.15$  g/kg respectively compared to  $3.16 \pm 1.49$  g/kg placebo group. After the first hours There were no significant differences among the five groups' p-values >0.05 (Figure1). After two hours, the food intake was significantly higher in chlorpromazine and lorazepam (0.5mg/kg and 1mg/kg) groups compared to placebo p-value <0.05. food intake among the treatment groups in chlorpromazine was significantly higher than lorazepam (1mg/kg , 2mg/kg) p-value <0.05 No significant differences were shown among the other groups at this time p-value>0.05(Figure 2). after 3 hours, the food intake was significantly higher in chlorpromazine and lorazepam(0.5mg/kg and 1mg/kg) groups compared to the placebo p- value <0.05. chlorpromazine statistically significantly higher than food intake compared to the treatment groups p-value <0.05. lorazepam(0.5mg/kg) was significantly higher than food intake compared to other lorazepam groups p-value <0.05. No significant differences were shown among different groups at this time p-value >0.05(Figure 3). After 4 hours, the food intake was significantly higher in chlorpromazine and lorazepam (0.5mg/kg,1mg/kg) groups compared to placebo p-value <0.05. lorazepam(1mg/kg), and chlorpromazine groups were significantly higher than food intake to lorazepam(2mg/kg) p-value <0.05.No significant differences were shown among the other groups at this time p-value >0.05(Figure 4). After 5 hours, the food intake was significantly higher in chlorpromazine compared to the placebo group p-value <0.05. lorazepam(1mg/kg), and chlorpromazine groups were significantly higher than food intake to the lorazepam(2mg/kg p-value <0.05 no significant differences were shown among the other groups at this time p-value >0.05(Figure 5). Food consumption was considerably greater in the chlorpromazine group after 6 hours compared to the placebo group (p-value 0.05). At this time, no significant differences were seen between the other groups (p-value >0.05) (Figure 6). After 7 hours, the food intake was significantly higher in chlorpromazine compared to other groups p-value <0.05. No significant differences were shown among the different groups at this time p-value >0.05 (Figure7). After 8 hours, the food intake was significantly higher in chlorpromazine compared to other groups p-value <0.05. No significant differences were shown among the other groups at this time p-value >0.05 (Figure 8) after 12 hours of administration of lorazepam (0.5mg/kg ,1mg/kg ,2mg/kg) or chlorpromazine was  $131.57 \pm 22.66$  and  $130.89 \pm 23.63$  g/kg and  $118.49 \pm 24.52$  g/kg and  $159.79 \pm 20.29$  g/kg respectively compared to  $142.52 \pm 16.72$  g/kg of placebo group. There were no significant differences between the five groups p-value >0.05(Figure9).

Half to First hour, after the administration of lorazepam (2mg/kg,1mg/kg,.05mg/kg), 4 of 6 birds, 4 of 6 birds, 2of 6 birds respectively, show signs of moderate sedation by head drooping and eye closure. The chlorpromazine and placebo groups, on the other hand, showed no symptoms of sedation. Mild sedative effects persisted in the Lorazepam groups for two hours.

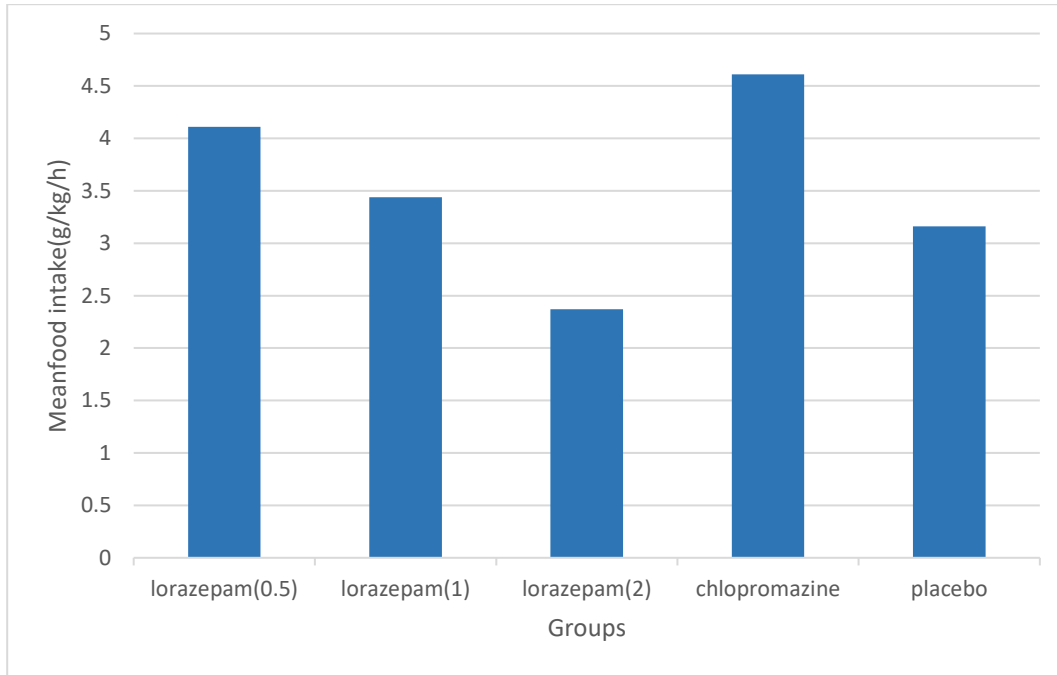


Figure 1. Mean food intake one hours after drug administration (g/kg/hours) were not significantly different among the treatments compared to placebo group p-value >0.05

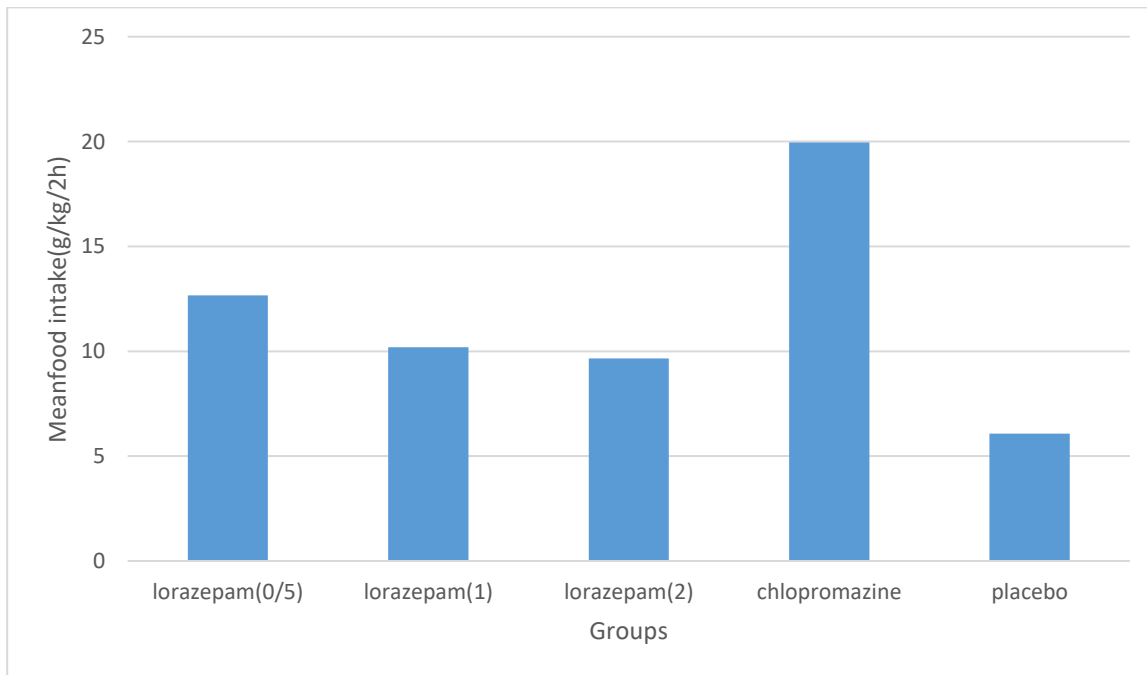


Figure 2. Mean food intake two hours after drug administration (g/kg/2hours) was significantly higher in the chlorpromazine and lorazepam (0.5mg/kg and 1mg/kg) groups compared to placebo p-value <0.05. food intake among the treatment groups in the chlorpromazine significantly higher than lorazepam (1mg/kg ,2mg/kg) p-value <0.05.No significant differences were shown among the other groups at this time p-value >0.05

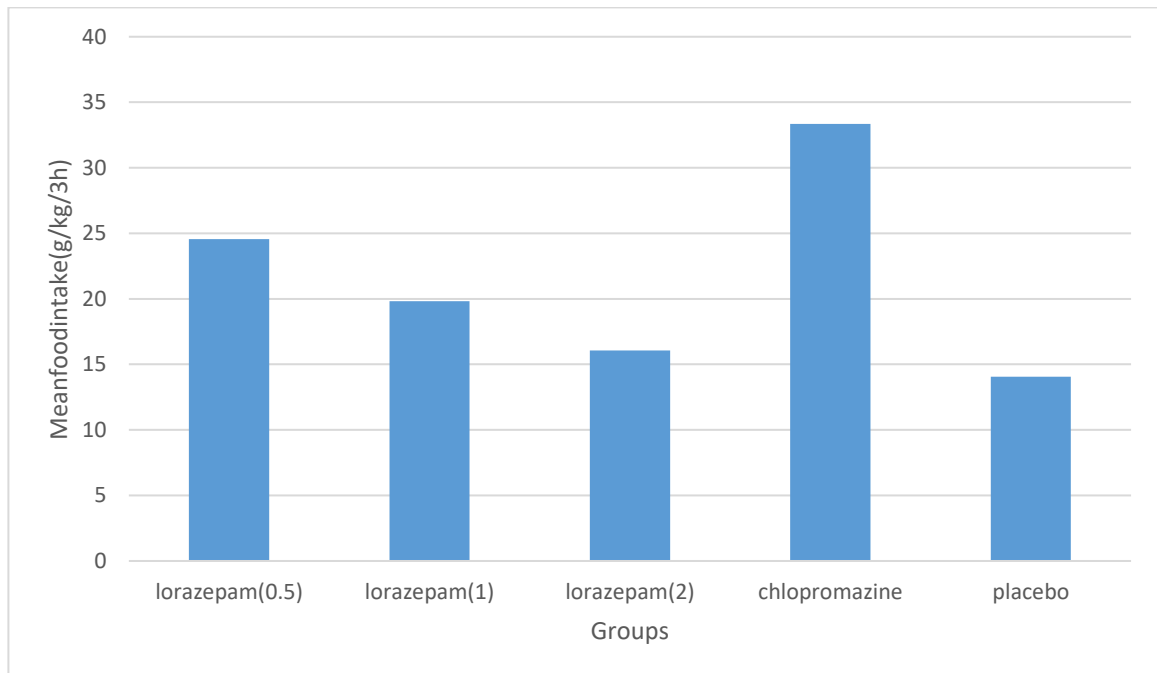


Figure 3. Mean food intake three hours after drug administration (g/kg/3hours) was significantly higher in the chlorpromazine and lorazepam (0.5mg/kg and 1mg/kg) groups compared to the placebo p-value <0.05. chlorpromazine significantly higher than food intake compared to the treatment groups p-value <0.05. Lorazepam(0.5mg/kg) was significantly higher than food intake compared to other lorazepam groups p-value <0.05. no significant differences were shown among the other groups at this time p-value >0.05

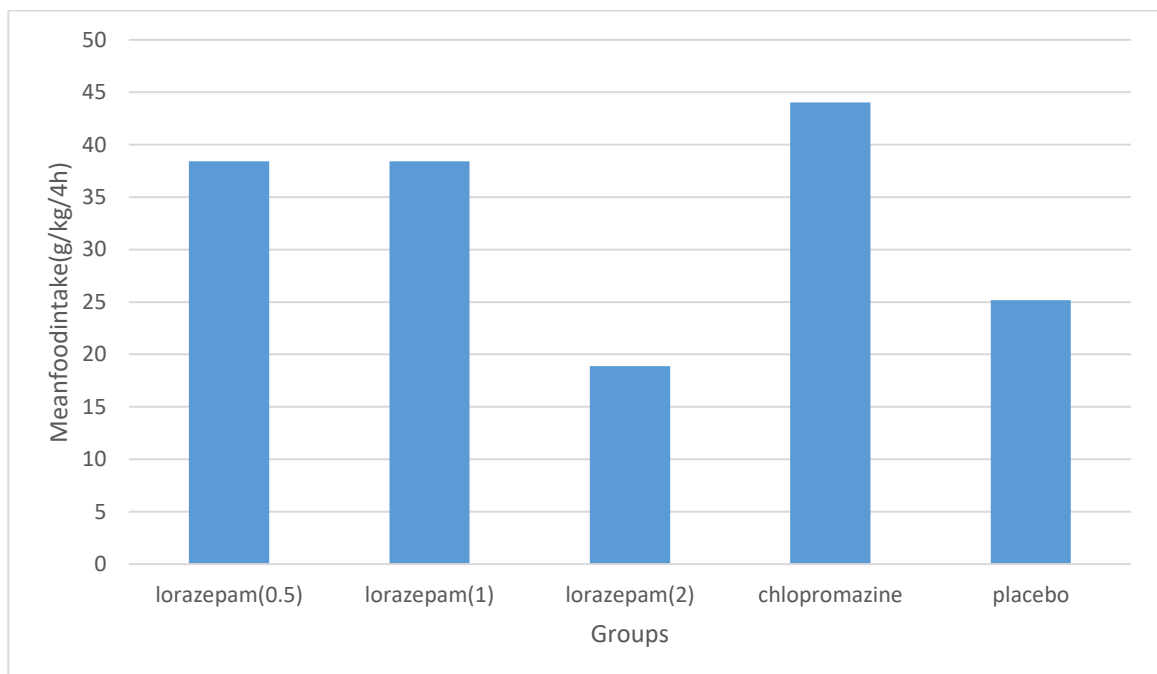


Figure 4. Mean food intake four hours after drug administration (g/kg/4hours) was significantly higher in chlorpromazine and lorazepam (0.5mg/kg,1mg/kg) groups compared to placebo p-value <0.05. lorazepam(1mg/kg), and chlorpromazine groups were significantly higher than food intake to

lorazepam(2mg/kg) p-value <0.05.No significant differences were shown among the other groups at this time p value>0.05

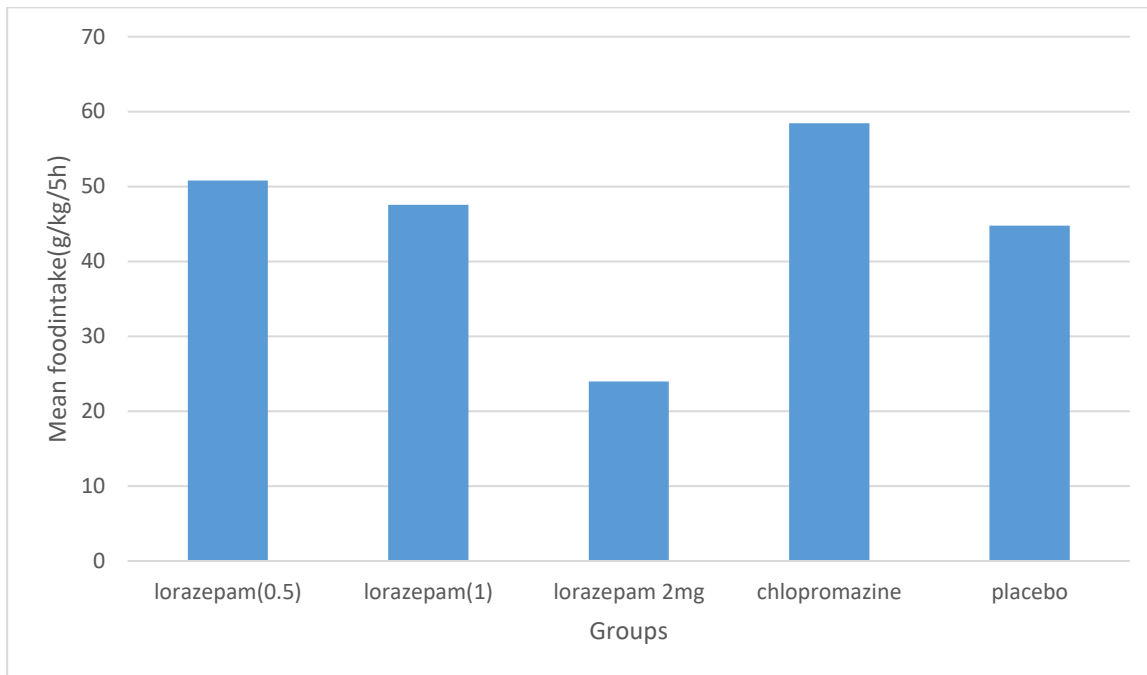


Figure 5 Mean food intake three hours after drug administration (g/kg/5hour) was significantly higher in the chlorpromazine compared to the placebo group p-value <0.05. lorazepam(1mg/kg) and chlorpromazine groups were significantly higher than food intake to the lorazepam(2mg/kg) p-value <0.05. No significant differences were shown among the other groups at this time p-value >0.05

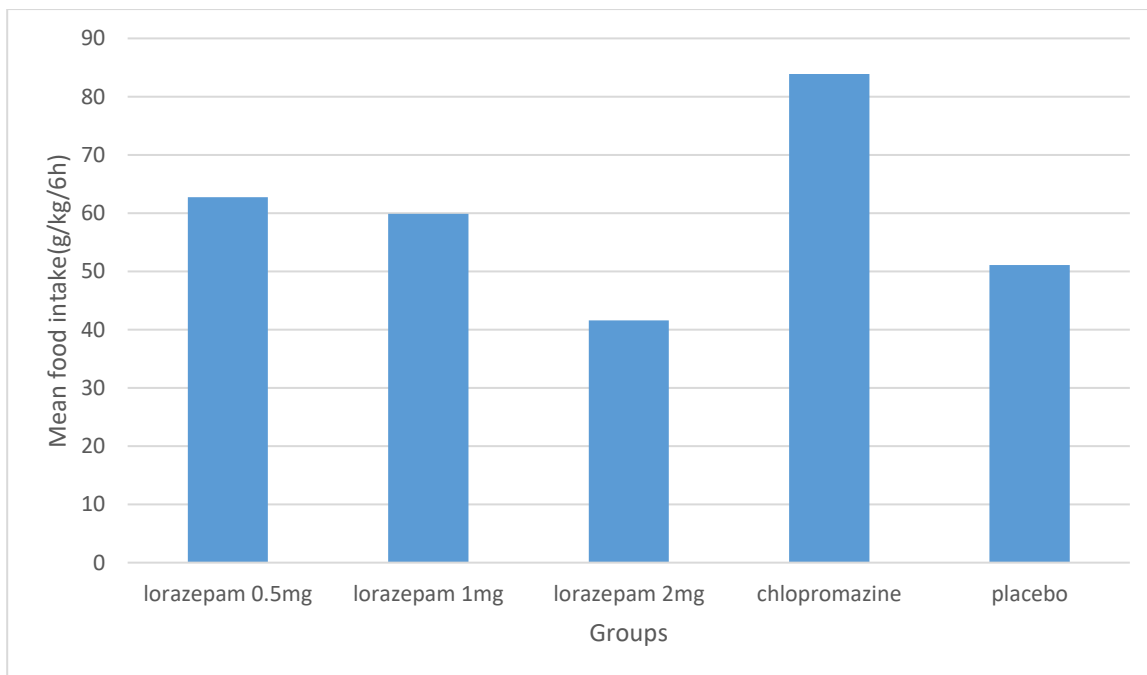


Figure 6. mean food intake six hours after drug administration (g/kg/6hours) was significantly higher in the chlorpromazine to placebo group p-value <0.05. No significant differences were shown among the other groups at this time p-value >0.05

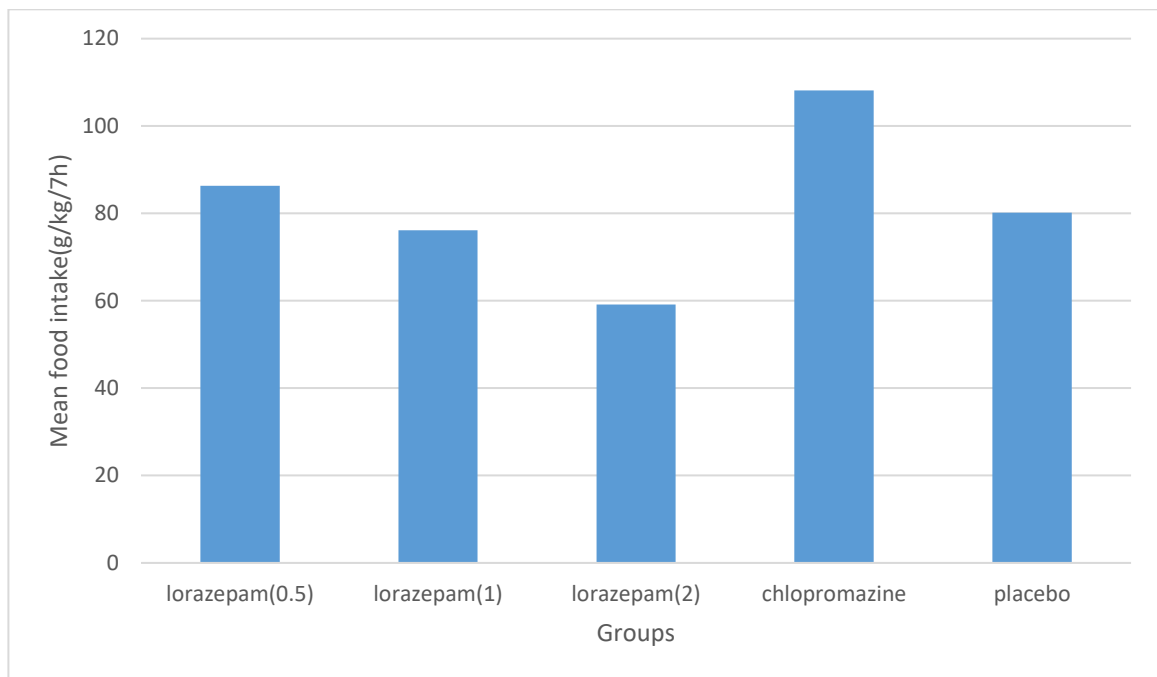


Figure 7. Mean food intake seven hours after drug administration (g/kg/7hours) was significantly higher in the chlorpromazine compared to other groups p-value <0.05. No significant differences were shown among the other groups at this time p-value >0.05

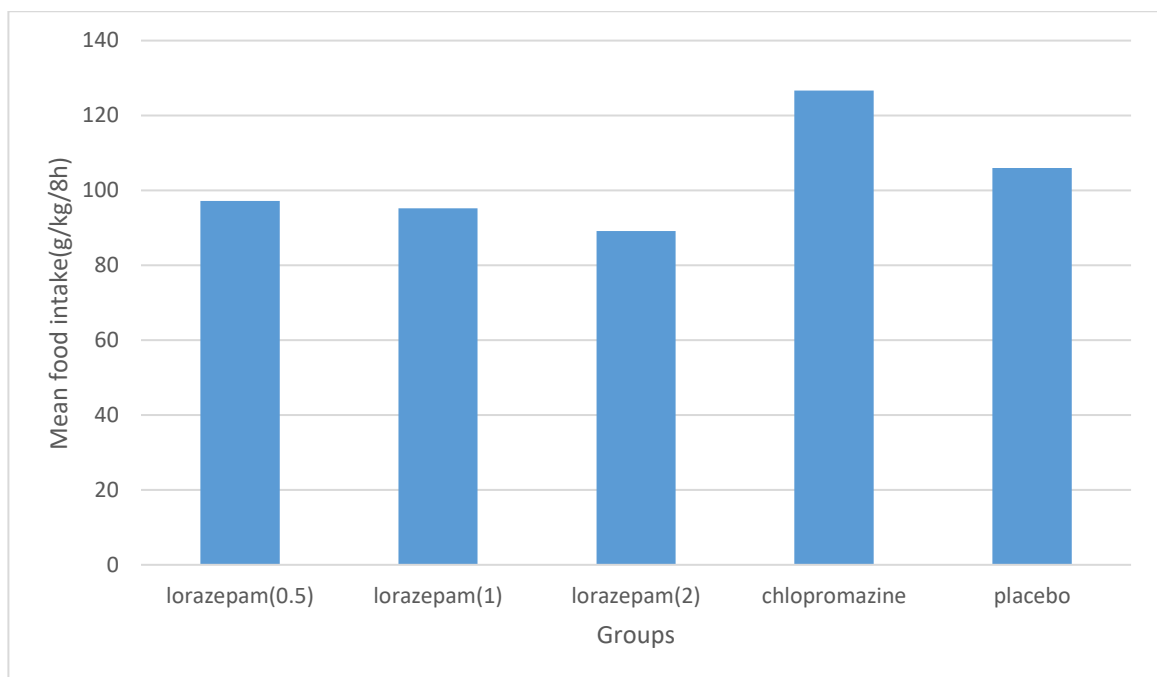


Figure 8. Mean food intake eight hours after drug administration (g/kg/8hour) was significantly higher in the chlorpromazine compared to other groups p-value <0.05. No significant differences were shown among the other groups at this time p-value >0.05

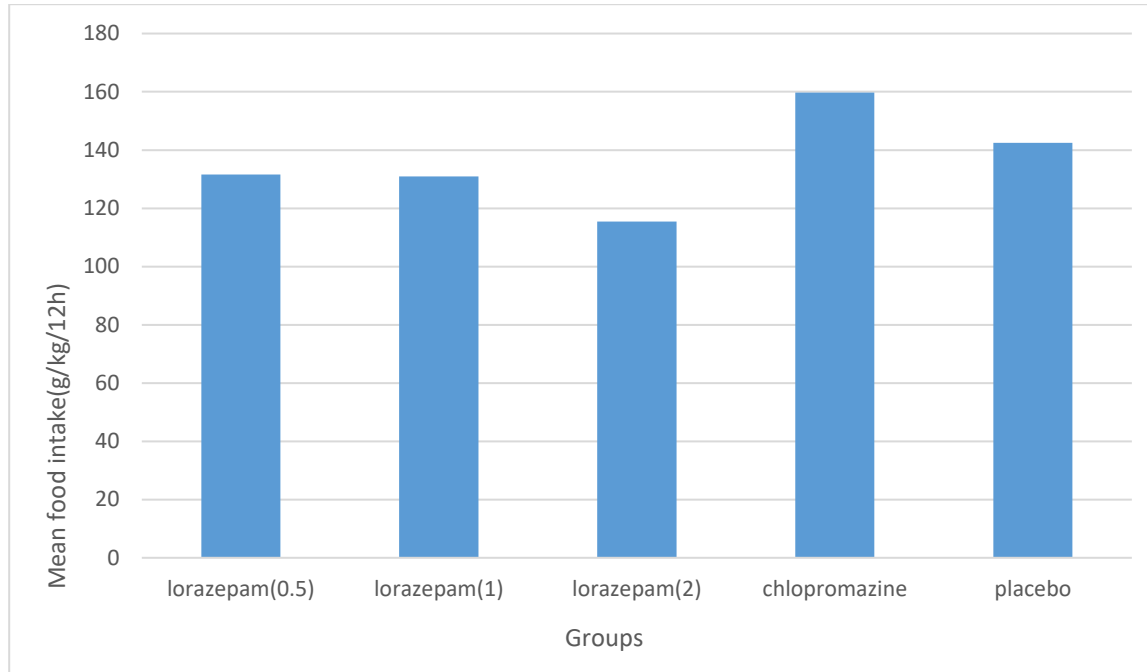


Figure 9. Mean food intake twelve hours after drug administration (g/kg/12hour) was not significantly different among the five groups p-value >0.05

## Discussion

In the current research, individuals' food intake increased significantly after receiving pectoral intramuscular injections of lorazepam and chlorpromazine in budgerigars. Comparing lorazepam (0.5 mg/kg, 1 mg/kg) to placebo, food intake increases four hours after the drug is administered. This result is almost accordant, with other study which reported that midazolam, and lorazepam(1mg/kg) increase cumulative food intake for the first 5 hours in budgerigars.[17]. However, our study shows that lorazepam does not lead to an increase in appetite in the first hour after administration and this increase in appetite remains until 4 hours later. It seems that the reason for this contradiction was probably caused by the anxiety conditions because in the previous study, the birds were transferred from wire enclosure(76×46×46cm) to the mouse cage(29×19×18 )(anxiety state).But in our study, animals were transferred from wire enclosure(76×46×46cm) to the wire enclosure(38×38×28cm) (Non-anxious state), which is consistent with this finding that food intake in marmosets that received midazolam was increased in transport cage( anxiety state), but not in the home cage( Non-anxious state) compare to placebo[6]. A lower dosage of lorazepam(0.5mg/kg) higher than increasing appetite in the budgerigar compare to lorazepam(1mg/kg,2mg/kg).lorazepam(2mg/kg) has no effect increasing appetite in budgerigar.The appetizing effects of low- dose benzodiazepines were mentioned in some past studies[14, 15]. Whereas the intramuscular absorption of lorazepam or midazolam is swift and flawless, the absorption of diazepam or chlordiazepoxide is quiet and inconsistent. [19]. Central nervous system toxicity and systemic unpleasant effects are The majority usual side effects of benzodiazepines. Other side effects included Respiratory depression with bradypnea, hypotension, and drowsiness[18]. No adverse effect were noted following the lorazepam (0.5mg/kg,1mg/kg,2mg/kg) dose in the current study. Sedation behavior included eye closure and head drooping in the lorazepam groups, were more severe than the others and were dose-dependent, and continued until two hours after the injection. Food intake in the chlorpromazine group is significantly higher than the placebo, and other treatment groups, the duration of increased appetite in the chlorpromazine group is up to 8 hours, while in the lorazepam (0.5mg/kg,1mg/kg) is up to four hours.Various studies show that antipsychotic drugs lead to an increase in appetite, and weight gain



in human and animals[19-23]. A study, it was shown that in humans, the risk of weight gain with antipsychotic drugs is more than 7%, compared to more than 5% with antidepressants. But some of them, like aripiprazole, lurasidone, and quetiapine, did not lead to a clinically significant weight gain of  $\geq 7\%$ [24]. since that most anorexic birds are lethargic, the use of benzodiazepine drugs creates limitations in terms of the sedative effects in addition they have short term increase appetite in budgerigar, while chlorpromazine at the 0.1mg/kg IM dose, does not cause sedative effects, which have a more and longer increase appetite in budgerigar compare to lorazepam so will be high benefits in the clinic in order to reduce repetition injections, and side effects of the drug in psittacine birds. Future research need to evaluate how other antipsychotics affect psittacine birds' food intake and how chlorpromazine affects other psittacine species' hunger. It is suggested that the effect of antipsychotic drugs, and benzodiazepines on food intake under six months of age birds be conducted in the subsequent study

**Conclusion.** Intramuscular administration of chlorpromazine has the best result on increasing food intake compared to lorazepam without any sedative effect in the healthy budgerigars. A lower dosage of lorazepam(0.5mg/kg) has more increased appetite on food intake with less sedative effect compared to other doses of this drug.

#### Author Contributions Statement

Amir safi: study idea, study design, data analysis, manuscript preparation; Hossein Hosseini: study idea, study design, data analysis, manuscript preparation; study design, data analysis, manuscript preparation

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