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Different effects of Bifeprunox, Aripiprazole, and Haloperidol on body weight gain, food and water intake, and locomotor activity in rats

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Abstract

Following on the success of Aripiprazole with its high clinical efficacy and minimal side effects, further antipsychotic drugs (such as Bifeprunox) have been developed based on the same dopamine D2 partial agonist pharmacological profile as Aripiprazole. However clinical trials of Bifeprunox have found differing results to that of its predecessor, without the same significant clinical efficacy. This study has therefore investigated the different effects of 10 week treatment with Aripiprazole (0.75 mg/kg, 3 times per day), Bifeprunox (0.8 mg/kg, 3 times per day) and Haloperidol (0.1 mg/kg, 3 times per day) on body weight gain, food and water intake, white fat mass, and 8 week treatment on locomotor activity. Treatment with Bifeprunox was found to significantly reduce all of the measured parameters except white fat mass compared to the control group. However, Aripiprazole and Haloperidol treatment reduced water intake compared to the control, without any significant effects on the other measured parameters. These findings further demonstrate the potential pharmacological differences between Aripiprazole and Bifeprunox, and identify potential weight loss side effects and increased anxiety behaviour with Bifeprunox treatment.

Title: Different Effects of Bifeprunox, Aripiprazole, and Haloperidol on Body Weight Gain, Food and Water Intake, and Locomotor Activity in Rats

Running title: Bifeprunox-induced decreases in body weight and locomotor activity

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Abstract

Following on the success of Aripiprazole with its high clinical efficacy and minimal side-effects, further antipsychotic drugs (such as Bifeprunox) have been developed based on the same dopamine D_2 partial agonist pharmacological profile as Aripiprazole. However clinical trials of Bifeprunox have found differing results to that of its predecessor, without the same significant clinical efficacy. This study has therefore investigated the different effects of 10 week treatment with Aripiprazole (0.75mg/kg, 3 times per day), Bifeprunox (0.8mg/kg, 3 times per day) and Haloperidol (0.1mg/kg, 3 times per day) on body weight gain, food and water intake, white fat mass, and 8 week treatment on locomotor activity. Treatment with Bifeprunox was found to significantly reduce all of the measured parameters except white fat mass compared to the control group. However, Aripiprazole and Haloperidol treatment reduced water intake compared to the control, without any significant effects on the other measured parameters. These findings further demonstrate the potential pharmacological differences between Aripiprazole and Bifeprunox, and identify potential weight loss side-effects and increased anxiety behaviour with Bifeprunox treatment.

Keywords: Antipsychotic, Aripiprazole, Bifeprunox, Haloperidol, body weight, locomotor activity

1. Introduction

First and second generation antipsychotic drugs (APD) are well-documented for inducing severe detrimental side-effects with varying treatment success rates for the symptoms of schizophrenia. First generation APDs (e.g. Haloperidol) induce severe extra-pyramidal side effects (EPS) [1-6] via a potent dopamine (DA) D_2 receptor antagonist mechanism. Second generation APDs (e.g. Olanzapine) potentially induce weight gain and other metabolic disorders (e.g. hyperlipidemia and type II diabetes) [7-11] via their action on multiple neurotransmitter receptors including histamine H_1, 5-HT_{2C} and muscarinic M3 receptors [1, 12-16].

Aripiprazole is regarded as a third generation APD with excellent therapeutic efficacy in controlling schizophrenia symptoms and a low incidence of EPS and weight gain side effects [17-20]. Although there are mixed reports on whether Aripiprazole has a DA D_2 partial agonist [1, 18, 21-24] or functionally selective mechanism of action [17, 25, 26], it has been found to exhibit a very high affinity (Ki value: 0.45 nM) [1, 14] and high occupancy rate (more than 90%) for D_2 receptors at the regular clinical dosage of 15-30 mg [1, 27, 28]. Although Aripiprazole has partial agonist and partial antagonist properties at 5-HT_{1A} and 5-HT_{2A} receptors respectively [1, 14, 17, 22, 25, 29], studies have found it to have low occupancy and activity levels at 5-$HT_{1A, 2A}$ receptors at therapeutic doses [18, 22, 30]. Following the success of Aripiprazole, a potential APD Bifeprunox (1-(2-Oxo-benzoxazolin-7-yl)-4-(3-biphenyl)methylpiperazinemesylate) was developed on the basis of the DA D_2 receptor partial agonist pharmacological model of Aripiprazole. Despite a similar partial agonist affinity for DA D_2 (Ki value: 8.5 nM) and 5-HT_{1A} receptors (Ki value: 5.2 nM) [31, 32], Bifeprunox was found to lack the therapeutic effects of Aripiprazole clinically, throwing

up questions as to the potential pharmacological differences between the two drugs [15, 33-36].

Aripiprazole has also been found to induce very limited to no weight gain side effects [1, 19, 26]. While there is no current evidence on Aripiprazole treatment alone decreasing body weight in both clinical and animal models, clinical studies have found it capable of reducing Olanzapine and Clozapine induced weight gain [37-39]. These studies report that after the weight gain seen with Olanzapine and Clozapine treatment, co-treatment with Aripiprazole over a period of 6 or 10 weeks is correlated with significant decreases in both body weight and body mass index. It is interesting that short term (6 weeks) Bifeprunox treatment significantly reduced body weight when compared to the control in two clinical trials [35, 40]. The pharmacological differences between Bifeprunox and Aripiprazole is currently unclear, with further knowledge into the differences between the two drugs potentially providing critical information towards the development of new APDs with a higher therapeutic efficacy and lower side effects. We have therefore investigated the effects of chronic treatment of Bifeprunox, Aripiprazole and Haloperidol (as a reference APD) on body weight gain, food and water intake, and locomotor activity in rats.

2. Materials and Methods
2.1. Animals and Housing

Male Sprague-Dawley rats (8 weeks old) were obtained from the Animal Resources Centre (Perth, WA, Australia). After arrival, the rats were housed in pairs for 1 week to adapt to the new environment before the study commenced. They were allowed *ad libitum* access to water and standard laboratory chow diet (3.9 kcal/g: 10% fat, 74% carbohydrate, 16% protein) throughout the experiment. During the experiment, they were housed in individual cages under environmentally controlled conditions (22°C, light cycle from 07:00 to 19:00 and dark

cycle from 19:00 to 07:00). All experimental procedures were approved by the Animal Ethics Committee, University of Wollongong, NSW, Australia (AE 11/02).

2.2. Drug Treatment

Before the drug treatment commenced, the rats were trained for self-administration drug treatment by feeding them cookie dough (0.3 g) without drugs 2 times per day for one week. Rats were randomly assigned into one of the following treatments (n = 12/group) for 10 weeks: (1) Aripiprazole (0.75 mg/kg, 3 times per day; Otsuka, Japan), (2) Haloperidol (0.1 mg/kg, 3 times per day; Sigma, Australia), (3) Bifeprunox (0.8 mg/kg, 3 times per day; Otava, Ukraine), or (4) control (vehicle, 3 times per day). Drugs were administered orally to the respective treatment groups by mixing cookie dough powder (containing sucrose 30.9%, cornstarch 30.9%, casein 15.5%, minerals 8.4%, fibre 6.4%, gelatine 6.3% and vitamins 1.6%), the drug, and a small amount of distilled water until even in consistency [26, 41]. The rats in the control group received an equivalent pellet without the drug. The dosages of Bifeprunox, Aripiprazole and Haloperidol in the current study used the dosage translation between species based on body surface area [42]. A 0.8 mg/kg Bifeprunox dosage in rats is equivalent to ~8 mg in humans (60 kg body weight), while 0.75 mg/kg Aripiprazole and 0.1 mg/kg Haloperidol is equivalent to ~7.5 mg and ~1 mg respectively; all of which are within the used/recommended clinical dosages [43]. It has been previously reported that, at these used dosages, Aripiprazole and Bifeprunox drug treatments reach about 90% DA D_2 receptor occupancy rates in the rat brains [32], while Haloperidol reaches approximately 70-80% DA D_2 receptor occupancy[44-46]. The drug dosages used in this study have been previously proven to be physiologically and behaviourally effective in rats and mice [26, 32, 47], whilst not causing any signs of extra-pyramidal side effects [32, 46]. The 0.3 g dry cookie dough pellets with or without drugs were fed to the rats 3 times per day (07:00h, 14:00h in the light phase and 22:00h in the dark phase; with 8±1 hour intervals) over the 10 week treatment

period. Rats were observed throughout the experiment to ensure that they completely consumed the cookie dough pellet and that there was no missing water or laboratory chow. Body weight and food and water intake were measured weekly.

2.3. Open Field Test

An open field test was performed on day 56 of the drug treatment to determine whether Aripiprazole, Haloperidol or Bifeprunox influenced the locomotor activity of rats, according to procedures used by our laboratory [41, 48, 49]. Briefly, a rat was placed in the centre of a black rectangular arena (60×60 cm^2, 40 cm high) exposed to an average lighting of 25 lux. A video camera recorded the behaviour of the rats for 30 minutes from the top of the arena. The locomotor activity of the rats was analysed using EthoVision Color-Pro software (Noldus Information Technology, Wageningen, The Netherlands). The total distance moved (cm), mean velocity (cm/s), rearing frequency, duration of time and frequency of entries into both the central and peripheral zones were measured.

2.4. Adiposity Measures

Following the 10 week treatment, all rats were sacrificed by carbon dioxide asphyxiation 2 hours after the last drug treatment. Post-mortem white adipose tissue (WAT), including perirenal, epididymal and inguinal fat, were dissected and individually weighed (g) [50, 51].

2.5. Statistical Analysis

All collected data were analysed using the SPSS (Windows version 19.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to examine the distribution of data from all experiments. Two-way repeated analysis of variance (ANOVA) (TREATMENT x DURATION as repeated measures) were applied to analyse body weight gain and food and water intake data. One-way ANOVA was used to examine behavioural and fat mass data. Multiple comparisons were performed using *post-hoc* Dunnett t-tests. Pearson's correlation

test was used to examine the relationships among the measurements. All data were expressed as mean ± standard error of the mean (SEM), and statistical significance was accepted when p < 0.05.

3. Results

3.1. Body Weight Gain

Two-way repeated ANOVAs (TREATMENT x DURATION as repeated measures) showed significant main effects of TREATMENT ($F_{3,48}$ = 5.423, p < 0.01) and DURATION ($F_{9,48}$ = 1241.065, p < 0.001) on accumulated body weight gain, as well as a significant interaction between TREATMENT and DURATION factors ($F_{27,48}$ = 5.471, p < 0.01; Figure 1A). A *post-hoc* Dunnett t-test indicated a significant decrease in the overall body weight gain of the Bifeprunox drug treatment group compared to the control over the 10 week duration of the study (-16.76%; p < 0.05). Further analysis on the weekly data revealed that Bifeprunox treatment significantly decreased body weight gain compared to the control, occurring in weeks 7, 9 and 10 (p < 0.05), with a trend to significance in week 8 of the treatment (p = 0.059). On the other hand, no significant differences in body weight gain were found in the Haloperidol (p > 0.05) and Aripiprazole (p > 0.05) groups compared to the control. Therefore, the 10 week drug treatment with Bifeprunox decreased body weight gain compared with the control group over the same time period.

3.2. Food Intake

Two-way repeated ANOVAs (TREATMENT x DURATION as repeated measures) showed significant effects of TREATMENT ($F_{3,48}$ = 3.224, p < 0.05) and DURATION ($F_{9,48}$ = 1593.634, p < 0.001) on accumulated food intake (Figure 1B). A significant interaction between TREATMENT and DURATION ($F_{27,48}$ = 3.284, p < 0.05) was also observed. *Post-hoc* analysis of overall food intake in the 10 week treatment period found a significant

decrease in total food intake in the Bifeprunox drug treatment group compared to the control (-15.40%; $p < 0.05$). This difference was significant from week 4, and lasted for the remainder of the study (all $p < 0.05$; Figure 1B). However no significant differences were found between any other drug treatment groups and the control (all $p > 0.05$). Thus, the Bifeprunox drug treatment significantly decreased the food intake of the animals when compared to the control group over the same time period. Furthermore, a significantly positive correlation was found between total body weight gain and total food intake ($r = 0.445$, $p < 0.01$; Figure 1D).

3.3. Water Intake

Two-way repeated ANOVAs (TREATMENT x DURATION as repeated measures) showed significant effects of TREATMENT ($F_{3,48} = 7.678$, $p < 0.001$) and DURATION ($F_{9,48} = 1943.238$, $p < 0.001$) on accumulated water intake, as well as a significant interaction between TREATMENT and DURATION ($F_{27,48} = 7.343$, $p < 0.001$). *Post-hoc* analysis of water intake data of the four groups for the entire 10 week treatment period is shown in Figure 1C. Significant decreases in total water intake were found in all of the drug treatment groups when compared to the control (Aripiprazole, -13.36%, $p < 0.05$; Haloperidol, -12.95%, $p < 0.05$; Bifeprunox, -25.59%, p < 0.001). Further analysis revealed this difference to be significant over the entire Bifeprunox treatment period (weeks 1-2, $p < 0.01$; weeks 3-10, $p < 0.001$), while the Aripiprazole and Haloperidol treatments decreased water intake from weeks 6 and 7 respectively for the remainder of the study period (both $p < 0.05$; Figure 1C).

3.4. Locomotor Activity

Behavioural testing results are shown in Table 1 and Figure 2. Analysis of locomotor activity via one-way ANOVA showed a significant effect of treatment on total distance moved (cm;

$F_{3,23}$ = 10.243, p < 0.001), average velocity (cm/s; $F_{3,23}$ = 10.306, p < 0.001), centre zone frequency ($F_{3,23}$ = 6.214, p < 0.01) and peripheral zone frequency ($F_{3,23}$ = 6.203, p < 0.01). Furthermore, a trend to significance was also found in the duration of the centre zone ($F_{3,23}$ = 2.577, p = 0.084) and peripheral zone ($F_{3,23}$ = 2.538, p = 0.087).

Post-hoc analysis of total distance moved showed a significant decrease in the Bifeprunox drug treatment group (-49.94%, p < 0.001), and a trend towards a significant decrease in the Haloperidol drug treatment group (p = 0.072) compared to the control (Table 1). A similar analysis of the average velocity also found a significant decrease in the Bifeprunox drug treatment group (-49.88%, p < 0.001), and a trend towards a significant decrease in the Haloperidol treatment group (p = 0.075) when compared to the control (Table 1). Statistically significant decreases in the Bifeprunox group compared to the control were also found in centre duration (-68.66%, p < 0.05), centre frequency (-69.00%, p < 0.01) and peripheral frequency (-69.80%, p < 0.01). No other significant differences were found in the other measured parameters between the other treatment groups and the control (p > 0.05).

3.5. Fat Deposits

Analysis via one-way ANOVA of fat deposit data (perirenal, epididymal and inguinal fat) found no significant effects on fat masses (perirenal fat, $F_{3,23}$ = 1.398, p = 0.273; epididymal fat, $F_{3,23}$ = 0.695, p = 0.566; inguinal fat, $F_{3,23}$ = 2.097, p = 0.133). Thus, the significant decrease in body weight found between the Bifeprunox and the control groups is not reflected in significant differences in body fat deposits.

4. Discussion

This was the first long-term study in an animal model to investigate the effects of Bifeprunox treatment on reducing body weight gain, food and water intake and locomotor activity. Our

results indicate a significant body weight loss in rats with long-term Bifeprunox treatment compared to the controls. This result is consistent with information documented in previous reports of short-term clinical trials on Bifeprunox treatment and its effects on body weight [35, 40]. Both of these clinical studies found significant reductions in body weight following 6 week 20 mg Bifeprunox treatment when compared to the control. The trial by Casey et al (2008) also showed statistically significant decreases in body weight in the lower 5 mg and 10 mg treatment groups. In this study, Bifeprunox treatment in rats also significantly decreased food intake compared to the control.

Aripiprazole treatment has been found to have limited, or no, body weight gain effects in humans [1, 8, 15, 19, 52-54]. The present study, with no significant weight changes observed in the rats with Aripiprazole treatment, is consistent with previous reports. In addition, these body weight gain results are reflected in recent animal studies reported from our laboratory [8, 52], showing that both short and long-term treatment with Aripiprazole (0.75 mg/kg, 3 times per day) resulted in no significant differences in weight gain compared to the control. However, although Aripiprazole has not been reported to cause body weight loss in clinical and animal studies, it has been reported to be clinically effective in reducing Olanzapine and Clozapine induced weight gain via a combination treatment with these drugs [37-39]. These results suggest a possible role of DA D_2 partial agonists or potential functionally selective properties of DA D_2 receptors in reducing weight gain. Food intake data also showed no significant differences between Aripiprazole (0.75 mg/kg, 3 times per day) treatment and the control in the present study. Similar results have been found in previous animal studies [8, 52].

The present study demonstrated that short- and long-term treatment with Haloperidol had no significant effects on body weight gain. These results are consistent with previous animal

studies over 12 week (long-term) treatment [55, 56]. Furthermore, no significant differences in the food or water intake data of the Haloperidol treatment groups were found compared to the control. This corresponds to previous animal studies indicating similar results of the effects of this DA D_2 receptor antagonist [8, 56].

Although Olanzapine was not examined in the present study, numerous recent results from our laboratory clearly demonstrate that Olanzapine significantly increases body weight gain [41, 51, 52]. It is interesting that Olanzapine increased weight gain and food intake after only 1 week treatment, however, it takes 6 weeks for Bifeprunox to be effective in reducing food intake and body weight. This suggests that different neural mechanisms induce the effects of these drugs on food intake and weight gain regulation. It has been shown that Olanzapine induced food intake and weight gain is largely through actions on the histamine H_1 [49, 52, 57] and serotonin (5-HT) 2C systems [54, 58, 59]. However, all of the drugs used in this study have a moderate affinity for the H_1 and $5\text{-}HT_{2C}$ receptors [1, 32, 34, 39]. In contrast, all of the drugs have a strong affinity with DA D_2 receptors: Haloperidol is a potent D_2 receptor antagonist, while Aripiprazole and Bifeprunox are both D_2 partial agonists. A clear disparity is present in the results of the Aripiprazole and Bifeprunox drug treatment groups compared to the control, with these differences potentially due to variation in the mechanisms of action of the 2 drugs.

While the exact reasons for the disparity in results between Bifeprunox and Aripiprazole on body weight and food intake are not known, different mechanisms of action on the DA D_2 receptors may be the reason for these variations. Studies have found different effects of the third generation APDs Aripiprazole and Bifeprunox on weight regulation and food intake, although both drugs are dopamine D2 partial agonists [35, 37, 38, 40]. Particular interest in these APDs is due to their actions in the mesolimbic DA pathway and partial agonist abilities

on the DA D_2 receptors [60-63]. As previously described, the dopamine system plays a critical role in numerous vital functions (e.g. reward, emotions and food intake). In particular, multiple aspects of the desire for more food have been linked to changes in neurotransmission along DA pathways, with strong similarities found between the biological mechanisms of desire for food and addiction to drugs [61-65]. Studies have found increases in DA projections along the striatal regions of the brain when normal weight, fasting subjects were tempted with food [60, 66], as well as decreases in striatal DA D_2 receptor availability inversely associated with the subject's body weight [60]. The observed variations in DA levels and D_2 receptor availability imply that the DA neurotransmission pathways play an important role in controlling the desire for food and hence body weight regulation [60-64, 66]. This suggests a potential role for DA partial agonists (e.g. the APDs Aripiprazole and Bifeprunox) in controlling food intake by targeting the DA pathway. Partial agonist drugs may potentially be able to regulate DAergic transmission, hence controlling the desire for more food in the same way that their mechanism of action in schizophrenia patients leads to alleviation of symptoms. However, this raises the question why only Bifeprunox significantly affects weight loss although both drugs are dopamine D_2 partial agonists. One explanation is that the two drugs have different pharmacological profiles on dopamine D_2 receptors. In fact, many studies have proposed that unlike Bifeprunox, Aripiprazole is not only a D_2 partial agonist but also a functionally selective drug on D2 receptors [17, 67]. Data from the present study further establishes potential mechanistic differences between these two APDs previously thought to be very alike, with only Bifeprunox drug treatment reducing body weight gain compared to the control. Such disparities in pharmacological mechanisms of action may be the reason that Bifeprunox was withdrawn from stage 2 clinical trials and rejected by the FDA in 2007 [24], however, further investigations into the pharmacological

differences between the drugs may provide key information towards the development of APDs with a greater therapeutic efficacy and decreased detrimental side effects.

Although both Aripiprazole and Bifeprunox have no significant affinity for the histamine H_1 receptor subtype previously mentioned, they have a small partial agonist affinity for other receptors such as the $5-HT_{1A}$, $5-HT_{2A}$ and $5-HT_{2C}$ receptor subtypes [31, 32, 34, 36, 68, 69]. In particular, variations in Aripiprazole and Bifeprunox affinity for the $5-HT_{2C}$ receptor subtype may also contribute to the discrepancy in body weight and food intake data found in the present study, with the $5-HT_{2C}$ receptor antagonism by Olanzapine and Clozapine previously linked to food intake and body weight regulation [54, 58, 70].

A statistically significant decrease in the water intake of animals treated with Bifeprunox was also observed on a weekly basis throughout the drug treatment period when compared to the control. Furthermore, the present study found that Aripiprazole and Haloperidol treatment decreased water intake compared to the control group from weeks 6 and 7 respectively (although with less effect than Bifeprunox). Similar results have been previously observed with Haloperidol [52] but not with Aripiprazole drug treatment. This confirms that both the Aripiprazole and Haloperidol treatments were at pharmacologically effective doses, although they did not significantly affect food intake, body weight and locomotor activity. The differences in time course in which the effects on water intake are elicited further highlights potential pharmacological differences between these APDs. These results further establish potential mechanistic differences between Aripiprazole and Bifeprunox.

The present study also demonstrated that treatment with Bifeprunox significantly decreased locomotor activity, along with centre frequency and duration compared to the control group (Table 1). Although a decrease in locomotion following Bifeprunox treatment has been previously reported [71], this study is the first to demonstrate such effects with a decrease in

weight gain. Although the weight loss associated with Bifeprunox treatment might be largely due to a reduced food intake, decreases in centre duration and centre frequency along with the decreases in body weight gain, food and water intake may potentially indicate possible increases in anxiety levels with Bifeprunox drug treatment, although it has previously been found to have potential anti-anxiolytic actions [36, 72, 73]. Another potential explanation befitting the results is that Bifeprunox may potentially cause bradykinesia and/or problems with the initiation of movement. Although bradykinesia has not been reported previously in Bifeprunox treatment, it would subsequently lead to reductions in food and water intake, along with a reduced ability to move to the centre of the open field arena, all observed in the present data. Furthermore, trends towards a significant decrease in both total distances travelled and mean velocity between the Haloperidol treated groups and the control were also observed. Such results are potentially due to Haloperidol's well-documented movement-related side effects due to its potent and non-selective DA D_2 antagonism.

5. Conclusion

In conclusion, this study has clearly shown that long-term (10 week) treatment with Bifeprunox significantly reduces body weight gain, food and water intake and locomotor activity compared to the controls. Furthermore, Aripiprazole and Haloperidol treatment over the same duration had no significant effects on body weight and food intake compared to the control. With Bifeprunox and Aripiprazole previously thought to have similar partial agonist effects at the DA D_2 and 5-HT_{1A} receptor subtypes, and limited affinities for weight regulation linked to the histamine H_1 receptors, the difference in results may be due to a functionally selective mechanism of action of Aripiprazole compared to the DA D_2 and 5-HT_{1A} receptor partial agonist actions of Bifeprunox. The answer of functional selectivity would explain not only this discrepancy in the body weight/food intake results, but also the ability of Aripiprazole to treat symptoms of schizophrenia with significantly fewer side-

effects compared to other DA D_2 and 5-HT_{1A} partial agonists such as Bifeprunox. Another possible reason is the observed ability of Bifeprunox to significantly reduce locomotor activity along with centre frequency and duration, potentially due to increases in anxiety levels in a drug previously thought to have anti-anxiolytic actions. Further investigations is important to reveal the potential behavioural effects of Bifeprunox treatment on motor function and also anxiety, along with the mechanisms underlying the pharmacological differences between Aripiprazole and Bifeprunox drug treatments.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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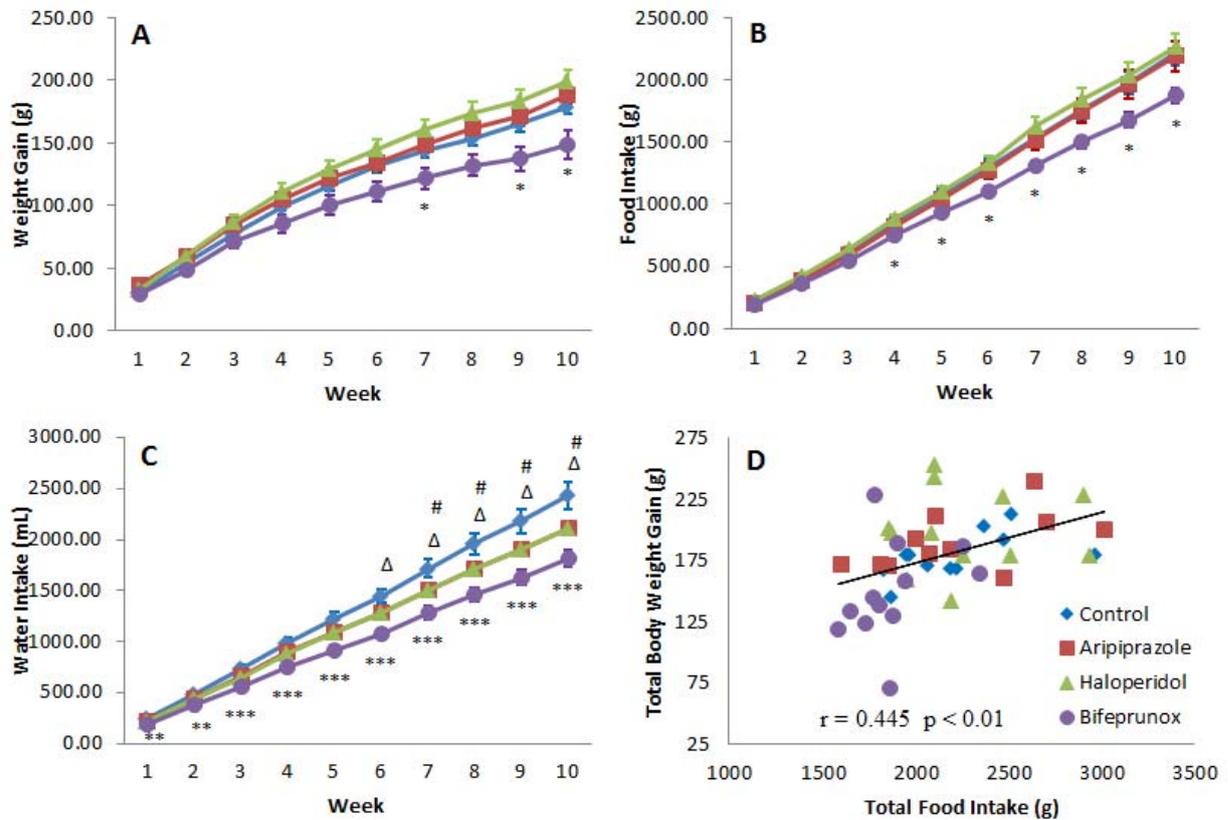
Figure Legends

Figure 1. (A) Cumulative body weight gain; (B) cumulative food intake; (C) cumulative water intake in male Sprague-Dawley rats treated with Aripiprazole (0.75 mg/kg, t.i.d; $n = 12$), Haloperidol (0.1 mg/kg, t.i.d; $n = 12$), Bifeprunox (0.8 mg/kg, t.i.d; $n = 12$) or control (vehicle; $n = 12$) for 10 weeks; (D) correlation between total food intake (g) and total body weight gain (g) . Abbreviations: t.i.d.: three times daily. *, $p < 0.05$, Δ, $p < 0.05$ Aripiprazole vs. control, #, $p < 0.05$ Haloperidol vs. control, **, $p < 0.01$ Bifeprunox vs. control, ***, $p < 0.001$ Bifeprunox vs. control.
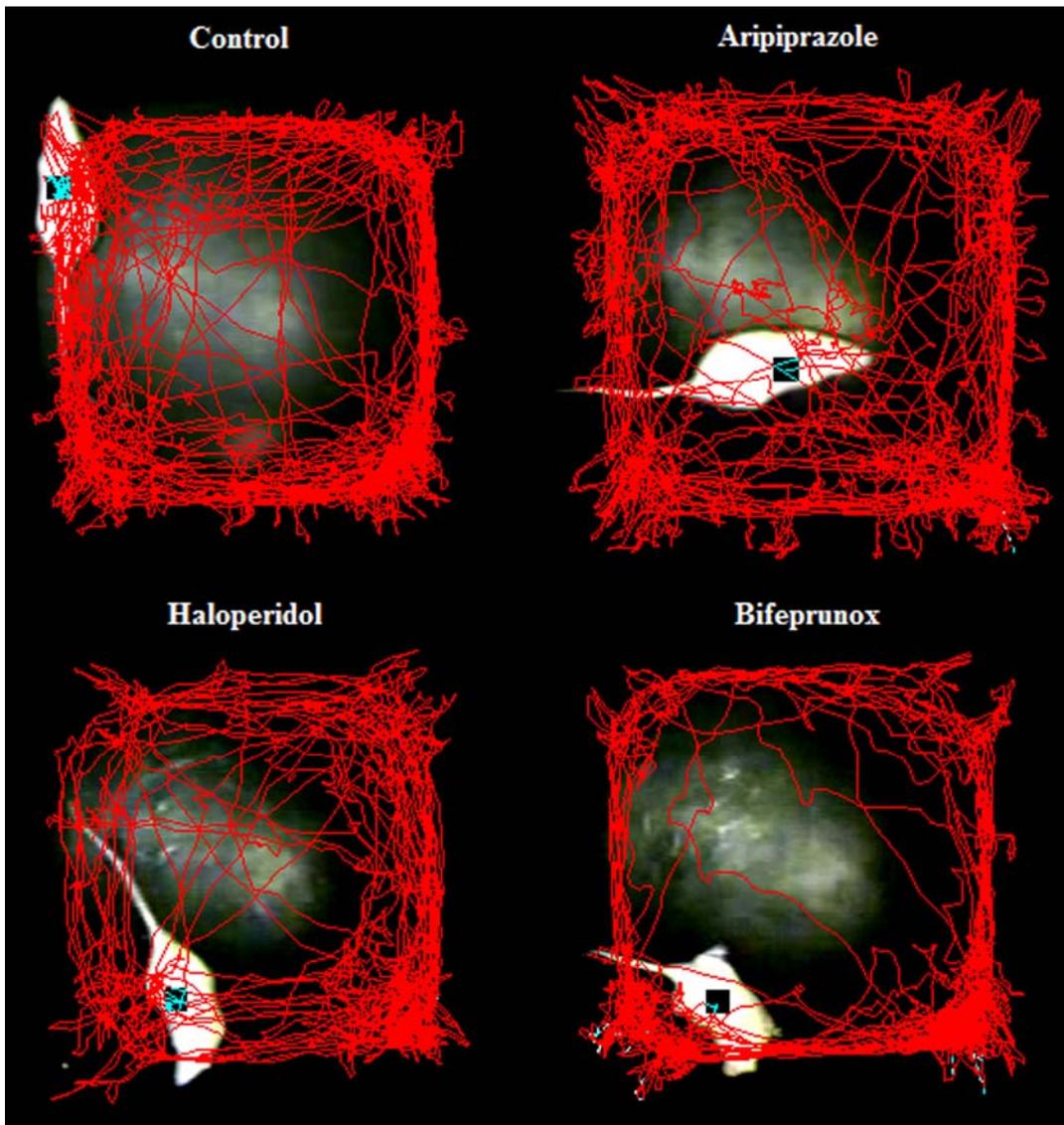
Figure 2. Examples of locomotor activity from rats treated with Aripiprazole ($n = 6$), Haloperidol ($n = 5$), Bifeprunox ($n = 6$) or control (vehicle; $n = 6$). Locomotor activity in the open field test was traced using EthoVision Color-Pro software.