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Research Article
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EVALUATION OF REBOXETIN AND FLUOXETIN ON OLANZAPINE INDUCED WEIGHT GAIN

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ABSTRACT

The present study was to evaluate the effect of Reboxetin and Fluoxetin on Olanzapine induced weight gain. Female Sprague dawly rats received, i) Olanzapine (4 mg/kg, b.i.d, i.p) alone, ii) Olanzapine + Reboxetin (10 mg/g, i.p), iii) Olanzapine + Fluoxetin (10 mg/kg, i.p) and distil water (per body wt) for 10 days and food intake, water intake and body weight gain was measured daily. Olanzapine show significant weight gain as compared to control from day-1 and kept on for six days followed by plateau. Reboxetin and Fluoxetin antagonized it at an equal intensity. Olanzapine induced increase in food consumption was strongly antagonized by Fluoxetin but Reboxetin did it up to control level. Water consumption was significantly increased by Olanzapine & strongly antagonized by Fluoxetin and Reboxetin kept it up to control level. The same results were obtained for food efficiency (gm body weight gain/ gm of food intake). The data suggest that Reboxetin antagonized weight gain equally as Fluoxetin did, without reducing food & water intake below normal level. So Reboxetin would be a good alternative to treat Olanzapine induced weight gain.

KEY WORDS

Fluoxetin; Olanzapine; Reboxetin

INTRODUCTION

It is clinically proved that atypical antipsychotic like Olanzapine & Clozapine rise body weight in patients[1,2,3,4], this effect switch on other undesirable conditions such as diabetes and other cardiac problems. Weight gain is main cause of patient incompliance for Olanzapine [5]. Olanzapine as an antipsychotic not only block dopaminergic receptors but also block muscarinic (M1-M5) receptors, serotonic (5HT-1A, 5HT-2C) receptors and histaminic (H1) receptors [6]. Weight gain, the major side effect is believe to be due to blockage of histaminic (H1) and serotonic (5HT-1A, 5HT-2C) receptors but there might be involvement of adrenergic receptors as well [7,8].

Reboxetin is a novel antidepressant drug. This drug acts by blocking presynaptic α2 adrenoceptors as result of that level of noradrenalin is increases in brain. Like other anorectic agents Reboxetin may reduce food intake and induce weight loss by activation of α1, β2 or β3 receptors [9].

Similarly serotonin plays a key role in weight regulation, food intake and water intake [10,11]. Fluoxetin, another antidepressant agent works by different mechanism. It works by blocking serotonin reuptake in the brain. Evatually, it raises the level of serotonin in the brain which leads to activation of different serotonic receptors.

So we hypothesized that Reboxetin and Fluoxetin may antagonize Olanzapine induced

weight gain in rats. We have also tried to find out the best drug from the two antidepressants.

MATERIALS AND METHODS

Animals

Female Sprague- dawley rats (200-250 gm) were maintained under standard husbandry conditions. Animals were exposed to a 12:00 hr light/12:00dark cycle with food and water provided at libitum. Each animal was fed standard rat chow (AMRUT LABS, Pune, Maharashtra, India, 22.5%protine; 4%Crude oil; 3%crude fibre; 3.62 kcal/gm metabolizable energy).

Drugs

Olanzapine; Reboxetin and Fluoxetin were used in present study.

Method

Olanzapine, dissolved in acidified water (pH 5.5 with citric acid) to a final concentration of 4 mg/ml was given daily via i.p route twice in a day 4.5 hr apart to all the groups[2]. One group received Reboxetin (10mg/kg, i.p) along with Olanzapine. Another group received Fluoxetin (10mg/kg, i.p) along with Olanzapine. Control received an equivalent amount of diluents as per body weight.

Body weight gain, food intake, water intake and food efficiency was measured daily.

Data Analysis

Analysis of variance (ANOVA) was used to determined difference among groups using INTA software (significance level, $p<0.05$). Data were presented as mean ± S.E.M.

Here Olanzapine group was compared with control group. Olanzapine+Reboxetin & Olanzapine+Fluoxetin groups were compared with Olanzapine group.

Sr.No.	Drug	Company
1.	Olanzapine	Zydus-Cadila
2.	Reboxetin	US Vitamins Pvt.Ltd.
3.	Fluoxetin	US Vitamins Pvt.Ltd.

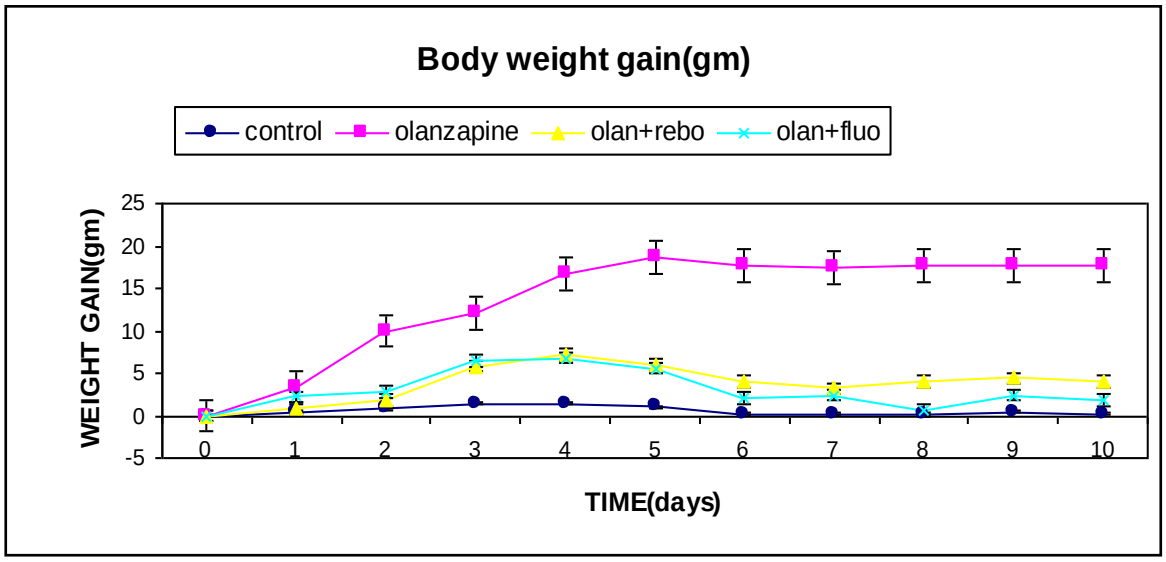
RESULTS

Olanzapine significantly increased body weight start from day-1 ($p<0.001$) which was significantly antagonized by Reboxetin ($p<0.01$) & Fluoxetin ($p<0.01$) [Graph No.1a][Table No.1]. Food consumption was significantly higher in Olanzapine treated group than control group ($p<0.01$). It was significantly antagonized by Reboxetin ($p<0.01$) & Fluoxetin ($p<0.001$) [Graph No.1b][Table No.2].

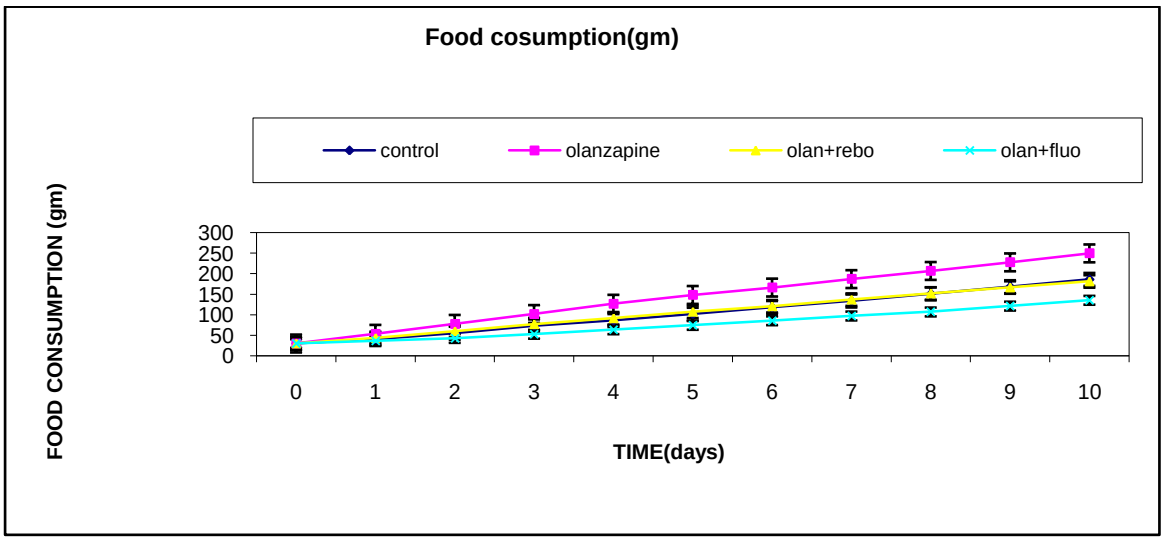
Water consumption was significantly increased by Olanzapine ($P<0.001$) starting from day-1. It was strongly antagonized Reboxetin ($P<0.001$) & Fluoxetin ($P<0.001$) [Graph No.1c][Table No.3]. Food efficiency was significantly increased by Olanzapine ($p<0.001$) and it was equally antagonized by Reboxetin ($p<0.001$) & Fluoxetin ($p<0.001$) up to day-6 [Graph No.1d][Table No.4].

Daily comparison for body weight gain was shown in [Graph No.2a][Table No.5]. where Olanzapine show plateau in weight gain after day-6. It was strongly antagonized by both the drugs but effect of Fluoxetin was more prominent. Food consumption for Olanzapine was significantly increased up to day-6 [Graph No.2b] [Table No.6]. It was noticeably antagonized by Reboxetin ($p<0.01$) and Fluoxetin ($p<0.001$). The same results were obtained for food efficiency where it was increased significantly by Olanzapine ($P<0.001$) and antagonized by both Reboxetin ($P<0.01$) and Fluoxetin ($p<0.001$) [Graph No.2c][Table No.7].

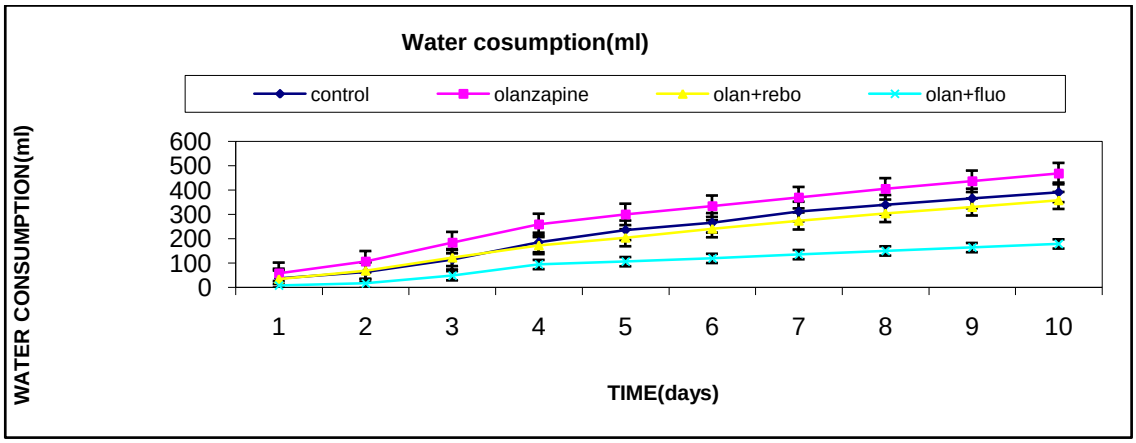
Graph No. 1a Body weight gain



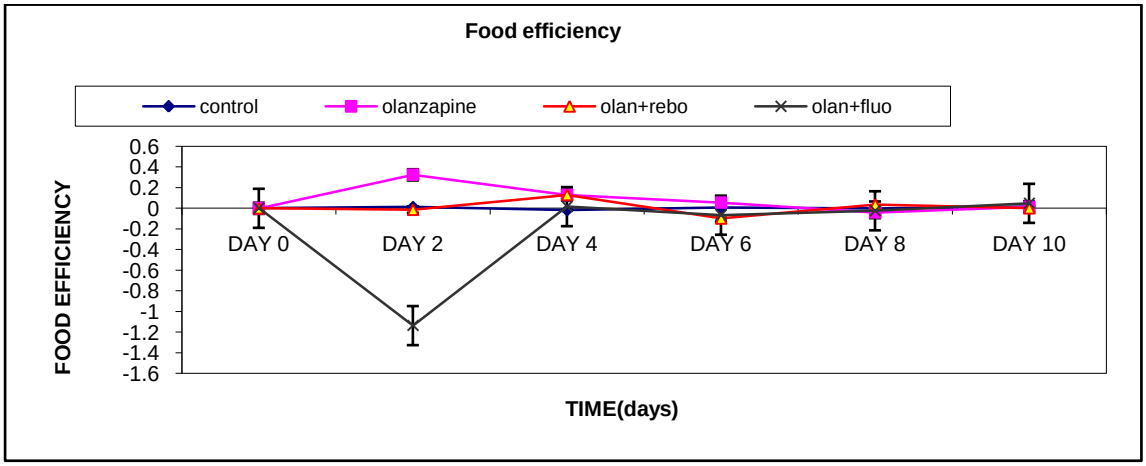
Graph No. 1b Food Consumption (gm)



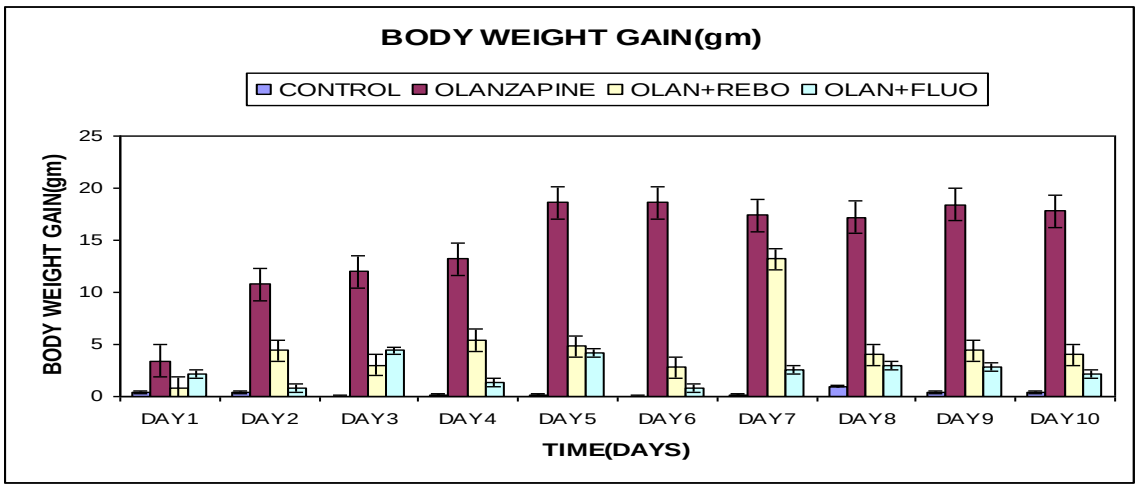
Graph No. 1c Water consumption



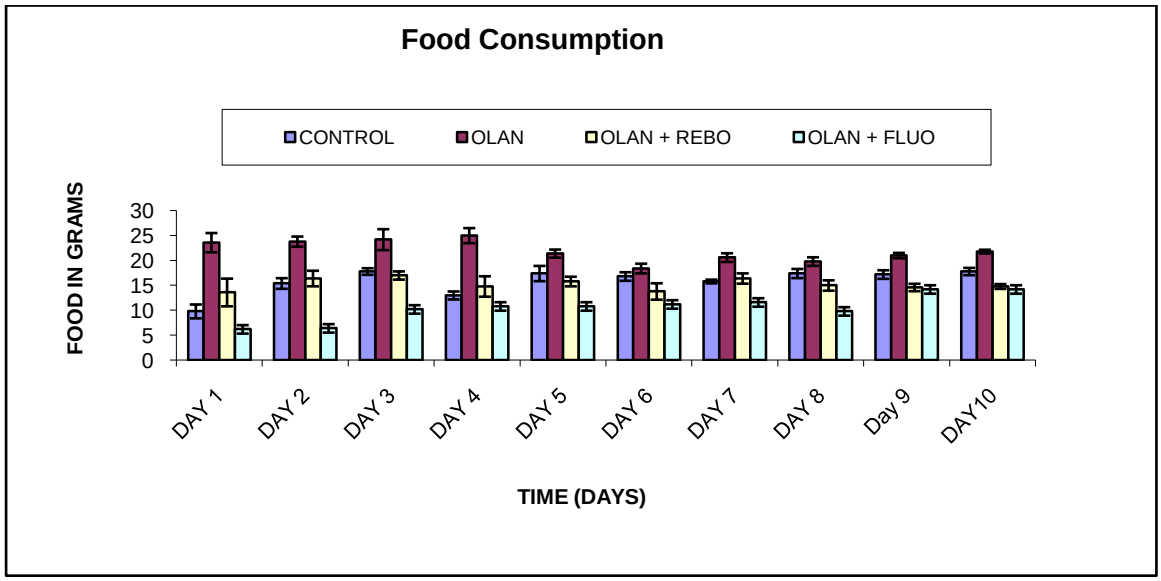
Graph No. 1d Food efficiency



Graph No. 2a Daily body weight gain



Graph No. 2b Daily food consumption



Graph No. 2c Daily water intake

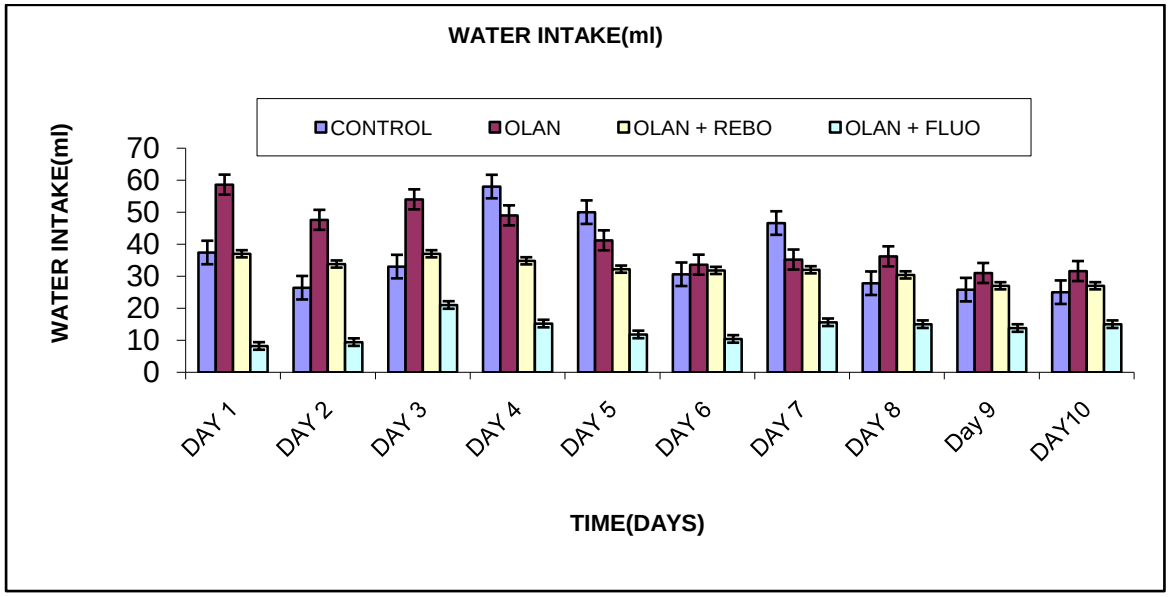


Table No.1 Daily Body Weight gain (gm)

Body Weight gain(gm)					
Sr No	**Days**	**Control**	**Olanzapine**	**Olan+Rebo**	**Olan+Fluo**
1	1	0.4 ± 0.24	3.4 ± 0.24	0.8 ± 0.26	2.2 ± 0.2
2	2	0.4 ± 0.24	10.8±. 0.37	4.4± 0.5	0.8± 0.37
3	3	0 ± 0.31	12 ± 0.83	3 ±. 0.44	4.4 ± 0.50
4	4	0.2 ± 0.58	13.2 ± 0.58	5.4 ± 0.81	1.4 ± 0.24
5	5	0.2 ± 0.37	18.6 ± 0.44	4.8 ± 0.37	4.2 ± 0.37
6	6	0 ± 0.31	18.6 ± 0.67	2.8 ± 0.37	0.8 ± 0.37
7	7	0.2 ± 0.58	17.4 ± 0.92	3.2 ± 0.48	2.6 ± 0.40
8	8	1 ± 0.44	17.2 ± 0.73	4 ± 0.44	3 ± 0.44
9	9	0.4 ± 0.40	18.4 ± 0.81	4.4 ± 0.50	2.8 ± 0.73
10	10	0.4 ± 0.40	17.8 ± 0.86	4 ± 0.31	2.2 ± 0.37

N=5,*p<0.05,**p<0.01,***p<0.001

Table No. 2 Daily Food intake (gm)

FOOD INTAKE(gms)					
SR NO	**DAYS**	**CONTROL**	**OLANZAPINE**	**OLAN+ REBO**	**OLAN + FLUO**
1	1	9.8 ± 1.39	23.6 ± 1.93*	13.6 ± 2.78	6.2 ± 2.20
2	2	15.4 ± 1.07	23.8 ± 1.02***	16.4 ± 1.56	6.4 ± 0.50***
3	3	17.8 ± 0.66	24.2 ± 2.10**	17 ± 0.83	10.4 ± 0.58**
4	4	13 ± 0.8	25 ± 1.51***	14.8 ± 2.05	10.8 ± 1.02
5	5	17.4 ± 1.53	21.4 ± 0.81	15.8 ± 0.96	10.8 ± 0.96
6	6	16.8 ± 0.86	18.4 ± 0.97	13.8 ± 1.65	11.2 ± 1.06*
7	7	15.8 ± 0.37	20.6 ± 0.87*	16.4 ± 1.03	11.6 ± 1.69
8	8	17.4 ± 0.92	19.8 ± 0.86	15 ± 1.04	9.8 ± 0.86***
9	9	17.2 ± 0.86	21 ± 0.547**	14.6 ± 0.74	14.2 ± 0.66*
10	10	17.8 ± 0.73	21.8 ± 0.37**	14.8 ± 0.48*	14.2 ± 0.66**

N=5,*p<0.05,**p<0.01,***p<0.001

Table No. 3 Daily Water intake (ml)

WATER INTAKE(ml)					
SR NO	**DAYS**	**CONTROL**	**OLANZAPINE**	**OLAN+REBO**	**OLAN+FLUO**
1	1	37.4 ± 1.32	58.6 ± 0.67***	37 ± 0.89	8.2 ± 0.37***
2	2	26.4 ± 2.42	47.6 ± 2.33***	33.8 ± 1.46	9.4 ± 0.4***
3	3	33 ± 1.30	54 ± 2.22***	37 ± 2.00	21 ± 1.30***
4	4	58 ± 2.28	49 ± 1.80**	34.8 ± 0.66	15.2 ± 1.02***
5	5	50 ± 1.30	41.2 ± 1.31	32.2 ± 0.8	11.8 ± 0.86
6	6	30.6 ± 1.28	33.6 ± 1.36	31.8 ± 1.65	10.4 ± 1.16***
7	7	46.± 1.32	35.2 ± 0.58***	32 ± 1.51	15.6 ± 1.50***
8	8	27.8 ± 1.15	36.2 ± 0.73***	30.4 ± 0.92	15 ± 0.7***
9	9	25.8 ± 0.58	31 ± 0.83***	27 ± 0.63	13.8 ± 0.37***
10	10	25 ± 0.94	31.6 ± 0.6***	27.0 ± 0.81	15 ± 0.83***

N=5,*p<0.05,**p<0.01,***p<0.001

Table No. 4 Food Efficiency

		Food Efficiency(Gm of weight gain\gm of food intake)			
Sr No	Days	control	olanzapine	olan+rebo	olan+fluo
1	0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
2	2	0.012 ± 0.002	0.324± 0.011	-0.014± 0.002	-1.136± 0.099
3	4	-0.018 ± 0.005	0.128 ± 0.008	0.128 ± 0.018	0.016 ± 0.002
4	6	0.006 ± 0.002	0.055 ± 0.002	-0.098 ± 0.006	-0.067 ± 0.0043
5	8	-0.004 ± 0.002	-0.041 ± 0.003	0.036 ± 0.004	-0.024 ± 0.005
6	10	0.016 ± 0.006	0.014 ± 0.005	0 ±0.003	0.048 ± 0.004

N=5,*p<0.05,**p<0.01,***p<0.001

Table No. 5 Cumulative Body Weight gain (gm)

		Weight gain(gm)			
Sr No	Days	Control	Olanzepine	Olan+rebo	Olan+fluo
1	0	0	0	0	0
2	1	0.4	3.4	0.8	2.2
3	2	0.8	10	1.8	2.8
4	3	1.4	12	5.8	6.4
5	4	1.4	16.6	7.2	6.8
6	5	1	18.6	6	5.6
7	6	0.2	17.6	4	2
8	7	0.2	17.4	3.2	2.4
9	8	0.2	17.6	4	0.6
10	9	0.4	17.6	4.4	2.4
11	10	0.2	17.8	4	1.8

N=5,*p<0.05, **p<0.01, ***p<0.001

Table No. 6 Cumulative food consumption (gm)

		Cumulative food consumption(gm)			
Sr No	Days	Control	Olanzepine	Olan+rebo	Olan+fluo
1	0	30	30	30	30
2	1	39.8	53.6	43.6	36.04
3	2	55.2	77.8	60	42.42
4	3	73	101.8	77	52.62
5	4	86	126.8	91.4	63.42
6	5	101.4	148.2	107.2	74.22
7	6	117.8	166.2	120.6	85.42
8	7	133.6	186.8	136.8	97.02
9	8	151	206.6	151.8	106.82
10	9	168.2	227.6	166.4	121.02
11	10	186	249.4	181.2	135.22

N=5,*p<0.05,**p<0.01,***p<0.001

Table No. 7 Cumulative water consumption (ml)

	Cumulative water consumption(ml)			
Days	**Control**	**Olanzapin**	**Olan+rebo**	**Olan+fluo**
1	37.4 ± 1.32	58.6 ± 0.67	35 ± 0.89	8.02 ± 0.37
2	63.44 ± 2.24	106.2 ± 2.33	68.8 ± 1.46	17.42 ± 0.40
3	114.25 ± 1.30	184.8 ± 2.22	123.2 ± 2.00	48.62 ± 1.30
4	185.25 ± 2.28	259.4 ± 1.80	172.4 ± 0.66	94.62 ± 1.02
5	235.25 ± 1.30	300.6 ± 1.31	204.6 ± 0.80	106.42 ± 0.86
6	265.85 ± 1.28	334.2 ± 1.36	241.6 ± 1.65	119.82 ± 1.16
7	312.45 ± 1.32	369.4 ± 0.58	273.6 ± 1.51	135.42 ± 1.50
8	340.25 ± 1.15	405.6 ± 1.73	304 ± 0.92	150.42 ± 0.70
9	366.05 ± 0.58	436.6 ± 0.83	331 ± 0.63	164.22 ± 0.37
10	391.05 ± 0.94	468.2 ± 0.60	358 ± 0.81	179.22 ± 0.83

N=5,*p<0.05,**p<0.01,***p<0.001

DISCUSSION

Data suggested that Olanzapine was rapidly inducing weight gain in female rats. Simultaneously it affects positively on food intake, water intake and food efficiency. The increment in weight gain was observed for 6 days, after wards plateau was observed. Mechanism for Olanzapine induced weight gain was not clear but it was believed that there might be involvement of $5HT_{2C}$, $5HT_{1A}$, Adrenergic (α_1, β_3) and histaminic (H_1) receptors[7,9,10,11.] The obesity promoting actions of Olanzapine might be associated with an increase in carbohydrate craving[11].

We had used different drugs having different mechanism of action to counteract Olanzapine induced weight gain.

Fluoxetin is an antidepressant agent which acts by inhibiting serotonin reuptake by neurons. It is showing strong antagonism on Olanzapine induced weight gain and other effects on food and water, which add another proof that 5HT receptors are equally responsible for food intake, water intake and weight regulation [7].

Reboxetin is selective α_2 inhibitor which increases level of noradrenalin in brain by preventing its neuronal reuptake. This high level of noradrenalin was responsible for antagonism of Olanzapine induced weight gain, water intake, and food intake and food efficiency. The reduction of food intake and water intake didn't go below control level which was observed with Fluoxetin but antagonism to weight gain was similar to Fluoxetin. This indicates that adrenergic receptors are highly involved in body weight regulation than food & water intake. There are evidences that addition of Reboxetin to conventional antipsychotic has been found to be safe and well tolerated in patients having schizophrenia [13]. Reboxetin is also antagonizing the negative symptoms of schizophrenic patients so combination of Olanzapine and Reboxetin is safe beneficial combination. The effect Reboxetin is only due to pharmacodynamic but not pharmacokinetic drug interaction because both the agents having modest effect on hepatic cytochrome enzymes [14,15]. So Reboxetin is having different ability for weight reduction and food, water intake. So we can assume that noradrenalin and serotonin have significant role in weight regulation.

CONCLUSION

From the data obtained for two different drugs Reboxetin and Fluoxetin, Fluoxetin is showing high degree of antagonism of Olanzapine's effect than Reboxetin. But Reboxetin is more preferable because it is having less effect on food and water intake which wasn't go below control level.

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