Abstract:
Aims and objectives - To evaluate the anorectic activity of Fluoxetine in male Wistar rats.

Materials and Methods - Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). The anorectic activity of Fluoxetine was studied in freely feeding male Wistar albino rats after 14 days of drug administration. Rats were randomly allocated to 2 groups, the control and the treatment, each consisting of 6 animals. The treatment group was administered Fluoxetine 8 milligram per kilogram once daily orally for 14 days. The body weight of each animal in the 2 groups was assessed before and after the 14 days treatment. Similarly food intake of each animal in both groups was measured after 14 days drug administration. Then the animals were allowed a wash out period of 45 days after which the two groups were crossed over and the same parameters were studied.

Results - The oral administration of Fluoxetine showed significant anorectic activity and reduction in the body weight compared to the control animals. The results were replicated by the observations after cross-over of the groups.

Conclusion - The present study shows that Fluoxetine, an SSRI which is clinically used as an anti-depressant has significant anorectic activity in animal model.

Keyword: Anorectic, Fluoxetine, freely feeding rats

Introduction:
Obesity is one of the worldwide health problems. WHO global estimate shows that about one tenth of world’s adult population are obese with over 200 million men and nearly 300 million women being obese. Obesity is one of the risk factors for many diseases like diabetes, hypertension, heart disease and osteoarthritis. Anorectics or appetite suppressants have a very important role to play in treatment of obesity. The serotonin and nor-adrenaline reuptake inhibitor, Sibutramine had been licensed as anti-obesity treatment for more than a decade. But potential cardiovascular adverse effects led to its withdrawal from market. It is well known that hypothalamus plays a key role in the mechanisms that control feeding behavior. Serotonin is one of the neurotransmitters in the brain which is an important mediator of satiety and also it modulates the mechanisms of control of feeding behavior.
and 5HT2C which are G-Protein coupled receptors have been specifically recognized as mediators of serotonin-induced satiety.4 Fluoxetine is a selective serotonin reuptake inhibitor that increases the brain synaptic levels of serotonin. Apart from serotonin reuptake inhibition, Fluoxetine has been found to alter the levels of orexigenic peptides, Neuropeptide Y & pro-opiomelanocortin.5,6 Previous studies so far done to investigate the anorectic activity of Fluoxetine were mostly done on food-deprived animals. But history of caloric restriction is said to up-regulate serotonin receptors imposing neurochemical changes that negatively impact feeding.7 The present study was therefore designed to assess the effects of Fluoxetine treatment on food intake and changes in body weight in freely feeding rat model.8

**Materials and Methods Drugs:**
Fluoxetine was obtained in the form of capsules containing 10 mg (Prodep) manufactured by Sun Pharma. This was diluted in 10 ml of sterile water (vehicle) to obtain 1mg/ml solution and appropriate dose was administered through oral route which was calculated based on body weight of each animal.

**Animals:**
Healthy adult male Wistar strain, albino rats of weight (150-300g) were used for the study. They were housed in standard polypropylene cages under room temperature (25±2C) and relative humidity (45 -55 %). They were exposed to 12:12 hr light-dark cycle. The rats were fed with standard rat pellet diet and water ad libitum.

**Animal ethics:**
The Institutional Animal Ethics Committee approved the protocol of the present study.

**Experimental design:**
The model used was normal adult male freely feeding rats of Wistar strain. Animals were divided into 2 groups, each consisting of 6 rats. The animals were randomly allocated to either group. **Group 1:** Control group ; Vehicle (sterile water) once daily per oral  **Group 2:** Treatment group ; Fluoxetine 8 mg/kg once daily per oral Control and treatment group rats were housed separately as 3 rats per cage using 2 cages for each group. Animals in both groups were weighed individually prior to the start of study. Group 1 animals were administered the vehicle and in group 2, the animals were treated with Fluoxetine every day for 14 days. During that period, every day, each of the animals in the two groups was briefly removed from cages and orally gavaged with either the drug or vehicle and returned back to their respective cages. All the animals were allowed access to standard rat pellet diet and water *ad libitum*. On day 14, after the drug administration, the animals were housed individually and allowed to acclimatize. On day 15 at 8 AM, after weighing the animals, a pre-weighed amount of food was left in cages to assess the food intake over 24 hour period. Next day at 8 AM, the weight of left-over food was measured. In order to obtain accurate measurements, the spilled over food at the bottom of the cages was returned to left-over food before being weighed. Amount of food intake was determined by the difference in weight of pre-weighted food to left-over food. As rodents consume most of their food in the dark phase, the 12 hour dark phase food intake is a very sensitive measure of food intake. Therefore food intake in the dark phase between 8PM to 8AM was also recorded.

**Cross over:**
The animals, after the estimation of food intake and body weight on day 15, were allowed a wash out period
of 45 days during which they were group housed in polypropylene cages and allowed standard pellet diet & water *ad libitum*. They were maintained in 12:12hr light dark cycle. After 45 days, the animals in the 2 groups, after being weighed individually, were crossed over so that the control group then became the treatment group and vice versa. The same parameters were recorded after similar treatment duration with the same dose of Fluoxetine given orally.

**Statistical Analysis**

All the data were expressed as mean ± standard deviation. The differences in food intake between the two groups and the changes in body weight in the test group as compared to the control group analyzed using "student t test". The data, before and after the cross-over of groups was analyzed using chi-square test for goodness of fit. p value < 0.05 was considered significant.

<p>| Table 1: Effect of Fluoxetine on food intake in rats after 14 days treatment |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>24 hr food intake(grams)</th>
<th>Dark phase food intake(grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake of control group</td>
<td>14 ± 2.00</td>
<td>12 ± 2.09</td>
</tr>
<tr>
<td>Food intake of treatment group</td>
<td>7.5 ± 2.88</td>
<td>7.16 ± 2.98</td>
</tr>
</tbody>
</table>

<p>| Table 2: Effect of Fluoxetine on body weight in rats after 14 days treatment |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight before treatment (grams)</td>
<td>249.50 ± 50.60</td>
<td>254.83 ± 37.08</td>
</tr>
<tr>
<td>Body weight after 14 days treatment (grams)</td>
<td>253.63 ± 43.85</td>
<td>252.16 ± 36.43</td>
</tr>
</tbody>
</table>

**Fig 3. Change in body weight of Control Vs Treatment group**

Applying t test for comparing the means of two independent samples, administration of Fluoxetine resulted in significant decrease in food intake over 24 hour period (p<0.01) as well as in the 12 hour
**Discussion:**
In the present study, we have investigated the effect of orally administered SSRI Fluoxetine on the body weight and food intake of freely feeding rats. The study has demonstrated a significant hypophagic as well as decrease in mean body weight in the treated group as compared to control animals. At a dose of 8 mg/kg, the anorectic effect was replicated after cross over. SSRIs increase the synaptic level of serotonin, an important mediator of satiety by inhibiting its reuptake. A substantial literature strongly supports the specific involvement of serotonin 5HT receptor subtypes in satiety and Fluoxetine administration in obese male Zucker rats has shown to increase pro-opiomelanocortin expression as well as increase in the numbers of alpha-Melanocyte Stimulating Hormone (α-MSH) positively immunostained neural cells in hypothalamic arcuate nucleus. Also altered mRNA expression levels of Neuropeptide Y and Corticotrophin Releasing Factor in hypothalamus could be a possible mechanism of Fluoxetine induced hypophagia and reduction in body weight of rats. The study results clearly point out that selective serotonin reuptake inhibitor like Fluoxetine is a potential target for anti-obesity treatments.

**Conclusion:**
Significant anorectic activity of Fluoxetine in animal model is brought out in this study. This however requires further evaluation in clinical studies to confirm the role of Fluoxetine as an appetite suppressant.

**References:**
1 WHO Health Statistics: April 2011.
7. Chandler-Laney PC, Castaneda E, Pritchett CE, Smith ML, Giddings M, Artiga Al, Boggiano MM.
