Chronic flibanserin treatment increases solicitations in the female rat.

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Background

- **Hypoactive sexual desire disorder (HSDD)**: prevalent disorder in pre- and postmenopausal women

- **Flibanserin** currently in Phase III, developed for the treatment of HSDD in women

- Proposed relevant experimental model for further **flibanserin** preclinical studies: measure of **proceptive** behaviors in the **female rat**
  - but needs further validation for use as predictive model
Female rat sexual behavior

**APPETITIVE / PROCEPTIVE behaviors**
Related to SEXUAL MOTIVATION

- genital investigation
- ear wiggling
- active solicitation
- hops and darts
- pacing

**CONSUMMATORY / RECEPTIVE behaviors**
Related to COPULATION

- lordosis response:
  - lordosis quotient
  - lordosis intensity

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*Homologous to women sexual desire*

*No counterpart to women sexual response*
Objective

Aim:
To assess the effects of flibanserin treatment on female rat sexual behavior.

General procedure:
Measure of proceptive and receptive behaviors in female rats during copulatory tests with sexually active male rats, in bilevel chambers.
Methods

1. 52 sexually naive Long Evans female rats

2. Females are ovariectomized and rendered sexually receptive by hormonal priming: estradiol (10µg) and progesterone (500µg) administered 48h and 4h respectively before the copulatory test.

3. 10 sexual training tests (T1 to T10) (30min) with sexually active males

4. 4 treatment groups (p.o., twice a day, for 29 days):
   - Flibanserin 5 mg/kg
   - Flibanserin 15 mg/kg
   - Flibanserin 45 mg/kg
   - Vehicle (0,5% Natrosol + 1% Polysorbate)

5. 5 treatment tests: (T11: acute treatment test, T12 to T15: once a week)
Methods

- All training and treatment tests videotaped and scored by experimenters blind to the treatment
Flibanserin enhanced active solicitations toward males

Number of solicitations before beginning of treatment (Baseline)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mean number</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Flib 5 mg/kg</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Flib 15 mg/kg</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Flib 45 mg/kg</td>
<td>14 ± 2</td>
</tr>
</tbody>
</table>

Number of solicitations after 15-days of treatment

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mean number</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Flib 5 mg/kg</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Flib 15 mg/kg</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Flib 45 mg/kg</td>
<td>16 ± 2</td>
</tr>
</tbody>
</table>

*** p < 0.001
** p < 0.01
* p < 0.05
Flibanserin did not modify other behavioral parameters after 15-days of treatment.

- **Number of hops and darts**
  - Vehicle: Mean = 2.0
  - Flib 5 mg/kg: Mean = 1.9
  - Flib 15 mg/kg: Mean = 2.1
  - Flib 45 mg/kg: Mean = 2.3

- **Lordosis quotient**
  - Vehicle: Mean = 1.00
  - Flib 5 mg/kg: Mean = 0.95
  - Flib 15 mg/kg: Mean = 1.00
  - Flib 45 mg/kg: Mean = 1.00

- **Number of level changes**
  - Vehicle: Mean = 120
  - Flib 5 mg/kg: Mean = 140
  - Flib 15 mg/kg: Mean = 150
  - Flib 45 mg/kg: Mean = 160

- **Number of ejaculations**
  - Vehicle: Mean = 2.0
  - Flib 5 mg/kg: Mean = 2.5
  - Flib 15 mg/kg: Mean = 2.0
  - Flib 45 mg/kg: Mean = 2.5
Flibanserin enhanced active solicitations toward males

**Number of solicitations after 22-days of treatment**

![Bar chart showing the number of solicitations after 22-days of treatment for different treatments.]

- Vehicle
- Flib 5 mg/kg
- Flib 15 mg/kg
- Flib 45 mg/kg

The chart shows a significant increase in the mean number of solicitations after treatment with Flibanserin compared to the vehicle and lower doses. The data is marked with asterisks to indicate statistical significance.
Flibanserin did not modify other behavioral parameters after 22-days of treatment.
SUMMARY

• 15-days of chronic 45 mg/kg flibanserin treatment results in a significant increase in female solicitations, compared to lower flibanserin doses (5 and 15 mg/kg) or vehicle

• This facilitatory effect of 45 mg/kg flibanserin on female solicitations is still observed after 22-days of chronic treatment

• Chronic flibanserin treatment did not modify other proceptive or receptive female sexual behaviors
CONCLUSION

These results evidence, for the first time, the prosexual effect of flibanserin in female rats receiving 45 mg/kg, twice daily administered for 15 days.

Since flibanserin has shown efficacy in treating premenopausal women with HSDD, these data combined suggest this animal model may be useful in supporting further pre-clinical drug studies for female sexual dysfunction.