Forced Swim Test

- When rats or mice are forced to swim in a deep cylinder with tepid water they become nearly immobile and cease trying to escape.

- Immobility is thought to reflect a state of “behavioral despair” and is reduced when rats and mice are treated with a wide variety of antidepressants.

- Rodent models of depression are mainly based on predictive validity, objectivity of measured response and their high reliability and reproducibility.
Ketamine Shows a Prolonged Effect in the Rat FS test

- Single injection of ketamine (10 mg/kg ip) after habituation session produces a long-lasting antidepressant-like effects in SD rats in the FS test.

![Graphs showing frequency of immobility, swimming, and climbing over time for Vehicle and Ketamine (10 mg/kg).](image)

*P<0.05, ~P<0.1
Effects of SSRI and Tricyclic Antidepressants

- The FS test in rats can differentiate between SSRI and Tricyclic-like antidepressants by their differential effects on climbing and swimming behaviors.

![Graph showing the effects of different treatments on behavior]

- Vehicle
- Fluoxetine 20 mg/kg
- Desipramine 20 mg/kg
Effects of Double and Triple Reuptake Inhibitors

- The triple uptake inhibitor DOV21947 and the 5-HT and NE reuptake inhibitor venlafaxine decreases immobility in the rat FS test.
Sertraline Decreases Time Immobile in Balb/cJ Mice

![Graph showing the decrease in time immobile with Sertraline compared to Vehicle.](image_url)
Differential Strain Responses to Sertraline in the FS Test

![Graph showing total time immobile (sec) for different strains and sertraline doses.]

- **C57BL/6J**
  - Vehicle
  - Sertraline 5 mg/kg
  - Sertraline 10 mg/kg
  - Sertraline 20 mg/kg

- **DBA/2J**
  - Vehicle
  - Sertraline 5 mg/kg
  - Sertraline 10 mg/kg
  - Sertraline 20 mg/kg

*Significant difference compared to Vehicle*
Tail Suspension in A/J mice

- Mice that are suspended by their tails become motionless.
- Clinically active typical and atypical antidepressants reduces this immobility

![Graph showing time immobile (sec) for different treatments: Vehicle, Buproprion 20 mg/kg, Desipramine 20 mg/kg, Fluoxetine 20 mg/kg. The graph indicates significant reductions in immobility for Buproprion and Fluoxetine compared to Vehicle and Desipramine.]
Marble Burying

• Marble burying is normally used as a model for both anxiety and obsessive compulsive disorder.

• Mice are placed individually in clean mouse cages containing approximately 6-cm of hard wood bedding and twenty black marbles placed in spaced rows of 5 for 30 min. Distance traveled during the test is captured by overhead cameras and quantified using Video Tracker Software (ViewPoint Life Sciences, France). After termination of the test the mice are removed from the cage and the number of buried marbles is counted. A marble is considered buried if it is pushed at least two thirds into the bedding.

• This test can be used to investigate pharmacological mechanisms through agonist/antagonists studies. It is also a useful test for yielding surrogate pharmacokinetic information on the duration of action of a drug.

• Mice pretreated antidepressants of various classes show less marble burying ability compared to the control mice.
Desipramine Decreases Marble Burying

- **Marbles Buried**
- **Total Distance Traveled (cm/30min)**

**Graphs show the decrease in marble burying and total distance traveled with Desipramine treatment compared to Vehicle.**

- **Vehicle**
- **Desipramine 5 mg/kg**
- **Desipramine 10 mg/kg**
- **Desipramine 20 mg/kg**

*Significant difference compared to Vehicle.*
Bupropion Decreases Marble Burying

Marbles Buried

Total Distance Traveled (cm/30min)
Paroxetine Decreases Marble Burying

Marbles Buried

- Vehicle
- Paroxetine 5 mg/kg

Total Distance Traveled (cm / 30min)

- Vehicle
- Paroxetine 5 mg/kg

* Indicates statistical significance.
Venlafaxine Decreases Marble Burying

Marbles Buried

- Vehicle
- Venlafaxine 10 mg/kg
- Venlafaxine 20 mg/kg

Total Distance Traveled (cm / 30min)

- Vehicle
- Venlafaxine 10 mg/kg
- Venlafaxine 20 mg/kg

* Indicates statistical significance.
Novelty Suppressed Feeding

- NSF measures a rodent’s aversion to eating in a novel environment.
- Chronic administration of imipramine decreases the latency to eat but does not impact home cage food consumption.
• Differential reinforcement of low rates of responding (DRL) is an operant test that requires behavioral suppression: the withholding of a response for a period of time such as 72 seconds (‘DRL72s’).

• DRL72s has predictive validity for antidepressant drugs. Administration of different classes of antidepressant (tricyclics, MAOIs, SSRIs) results in a decrease in response rate and an increase in reinforcement rate.

• Non-antidepressant drugs have different profiles of effects, such as, psychostimulants, which increase lever-presses and decrease reinforcers earned.
Tricyclic antidepressants increase the reinforcement rate and decrease the response rate

![Graph showing the effect of Imipramine Dose on Reinforcement and Response Rates](image1)

![Graph showing the effect of Desipramine Dose on Reinforcement and Response Rates](image2)
Chronic Social Defeat Stress (CSDS)

- Closely mimics the dynamic range of reactions that an individual can show in response to physical and psychological stressors.
- Ranges from the development of a major depressive disorder, post-traumatic stress disorder or resiliency to these disease states.
- Individual responses to stressors are particularly useful in modeling aspects of anxiety disorders such as PTSD with high construct, face, discriminative and predictive validity.
Schematic of CSDS Test

Experimental

New aggressor for 10 days

Aggressor

Physical Contact 5-10 min

Sensory Contact 24 hrs

Social Interaction

Control group goes through 24 hr sensory contact with same strain mouse

Control

Defeat
CSDS – Control and Defeat Phenotype

Social Interaction Score

Time in interaction zone (sec)

Time in corners (sec)
Effects of Imipramine on Social Deficits in Defeated Mice

- Oral administration of imipramine for 2 weeks attenuated social deficits in defeated mice.
- Acute administration of imipramine does not show efficacy in this model.
Ketamine Attenuates Social Deficits in Defeated Mice

Social Interaction Score

Control - Vehicle
Defeat - Vehicle
Defeat - Ketamine (10 mg/kg)

*
Sexual Dysfunction in Rats
Normal distribution of ejaculation frequency during 30min exposure to receptive female

- 'rapid' ejaculation (n=12)
- 'normal' ejaculation (n=12)
- 'delayed' ejaculation (n=12)

Ejaculation frequency

Number of animals

Std. Dev = 1.29  
Mean = 2.7
N = 99.00
Chronic Administration of Paroxetine Causes Sexual Dysfunction

**Total Number of Ejaculation**

<table>
<thead>
<tr>
<th>Day</th>
<th>Saline</th>
<th>Paroxetine 5 mg/kg</th>
<th>Paroxetine 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Latency for 1st Ejaculation (sec)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Saline</th>
<th>Paroxetine 5 mg/kg</th>
<th>Paroxetine 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates significant difference compared to control group.
Effects of Bupropion on Sexual Function

Latency to 1st Ejaculation

- **Vehicle**
- **Buproprion 15 mg/kg**

Day 1 | Day 7 | Day 14
--- | --- | ---
0 | 1000 | 500

Total Number of Ejaculations

- **Vehicle**
- **Buproprion 15 mg/kg**

Day 1 | Day 7 | Day 14
--- | --- | ---
0 | 3 | 2

*Significant difference.