Preclinical Tests For Depression
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 the effect of ketamine on immobility, swimming, and climbing over time.](image-url)
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.
**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

**Graphs:**
- **Time Immobile (sec):**
  - Two lines: Vehicle and Sertraline (20 mg/kg)
  - Time points: 1, 2, 3, 4, 5, 6 minutes
- **Total Time Immobile (sec):**
  - Comparison between Vehicle and Sertraline
  - Note: * denotes statistical significance.
Differential Strain Responses to Sertraline in the FS Test

![Graph showing Total Time Immobile (sec) for C57BL/6J and DBA/2J strains treated with different doses of Sertraline compared to Vehicle. The graph indicates significant differences (*) in immobility time between the treated groups and the Vehicle group.]
Tail Suspension in A/J mice

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

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

Total Distance Traveled (cm/30min)

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

* indicates significant difference from Vehicle control.
Bupropion Decreases Marble Burying

[Graph showing the effect of Bupropion on marble burying and total distance traveled in rodents. The graph displays bars for Vehicle, Bupropion 5 mg/kg, Bupropion 10 mg/kg, and Bupropion 20 mg/kg groups. Significant differences are indicated by asterisks (*) for each comparison.]

Marbles Buried

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

- Marbles Buried
- 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

* indicates a significant difference from the Vehicle group.

Total Distance Traveled (cm / 30min)

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

_Berton et al., 2006; Donahue et al., 2014._
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

![Graph showing Social Interaction Score]

Time in interaction zone (sec)

![Graph showing Time in interaction zone]

Time in corners (sec)

![Graph showing Time in corners]
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

![Graph showing social interaction score for different groups: Control - Vehicle, Defeat - Vehicle, and Defeat - Ketamine (10 mg/kg). The graph indicates that Ketamine (10 mg/kg) attenuates the social deficits observed in defeated mice.]

* indicates significant difference compared to Defeat - Vehicle group.
Sexual Dysfunction in Rats
Normal distribution of ejaculation frequency during 30min exposure to receptive female

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

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>Paroxetine 5 mg/kg</td>
<td>Paroxetine 5 mg/kg</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

### Latency for 1st Ejaculation (sec)

<table>
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<td>Paroxetine 10 mg/kg</td>
</tr>
<tr>
<td>500</td>
<td>1000</td>
<td>1500</td>
</tr>
</tbody>
</table>

* indicates statistical significance.
Effects of Bupropion on Sexual Function

Latency to 1st Ejaculation

- Vehicle
- Buproprion 15 mg/kg

Total Number of Ejaculations

- Vehicle
- Buproprion 15 mg/kg