# Characterization and optimization of rat models of osteoarthritis pain to profile novel assets in support of the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP)

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## Background

The National Institutes of Health Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠, Preclinical Screening Platform for Pain (PSPP) program aims to accelerate the discovery and development of new non-opioid, non-addictive pain therapeutics. Toward this goal, PSPP is collaborating with PsychoGenics, Inc. to validate preclinical models and endpoints to enable screening and profiling of assets, including small molecules, biologics, natural products, and devices. Here, we describe the validation of one such effort to evaluate and optimize the medial meniscal tear (MMT) and monoiodoacetate (MIA) models of osteoarthritis pain in the rat.

## Methods

**Animals:** Adult male and female Sprague Dawley rats (n=10, each sex) were used in these studies. All housing and testing of the animals were in accordance with the Principles of Laboratory Animal Care and the approval of PsychoGenics Inc., Institutional Animal Care and Use Committee in AAALAC-accredited facilities.

**Medial meniscal tear (MMT) model:** An incision of approximately 1 cm was made on the medial aspect of the left femoro-tibial knee joint, and the medial collateral ligament was exposed via blunt dissection under isoflurane anesthesia. The medial collateral ligament was transected to reflect the meniscus towards the femur, and the meniscus was cut through at its narrowest point to simulate a complete tear.

**Monoiodoacetate (MIA) model:** MIA (1 – 4.5 mg) was injected intraarticularly into the left hindlimb knee joint in preliminary studies, and based on the results from these studies, a dose of 1 mg of MIA was selected for subsequent studies. Rats were briefly anesthetized using isoflurane (1-5% to effect, inhalation) and received a single intraarticular injection of MIA (50 µl) into the left hindlimb knee joint through the patellar tendon using a 26 gauge needle attached to a 1 ml syringe.

**Hind paw tactile sensitivity:** Hind paw tactile sensitivity was measured by applying von Frey filaments (0.4, 0.6, 1, 2, 4, 6, 8, 15 g; Semmes-Weinstein, Stoelting, Wood Dale IL, USA) to the plantar hind paw and determining the paw withdrawal threshold (PWT) using the "up-down" method (Chaplan et al. 1994 J Neurosci Methods 53:55-63). A maximum of 9 filament applications were used to determine the 50% Withdrawal Threshold, and based on Chaplan et al. (1994), animals that did not respond to any filament were assigned a threshold of 15.0 g, while animals that responded to all filaments were assigned a threshold of 0.25 g. The PWT was determined for both the left and right hind paws, and assessments were made by a blinded investigator.

**Hind limb knee joint pressure sensitivity**: Knee joint sensitivity to a pressure stimulus was assessed using the Rodent Pincher Device (Bioseb). Rats were lightly restrained, the device was placed on the animal knee joint, and a progressive quantified squeeze force was applied across the joint. The force that elicited a response characterized by a knee withdrawal or vocalization was designated as the knee pressure response threshold (gm).

**Dynamic weight bearing**: Weight bearing on the hind paws of rats was assessed using the Dynamic Weight Bearing 2.0 Instrument (Bioseb). Rats were placed in the chamber for a period of 3 minutes per test where they were able to move freely. Hind paw weight bearing, in addition to other parameters (paw surface area, time on sensor pad), were recorded in real time and stored on a computer.

**Data analysis**: Data were analyzed using two-way repeated measures ANOVA with Bonferroni's or Dunnett's post hoc test when appropriate. Effects with $p<0.05$ were considered to be statistically significant. Power analysis and effect size were determined using SAS/STAT, and appropriate sample size was based on a power value of 0.8 to ensure adequate power for F-tests for two-way interactions. Data are represented from individual animals and are summarized as mean±sem.

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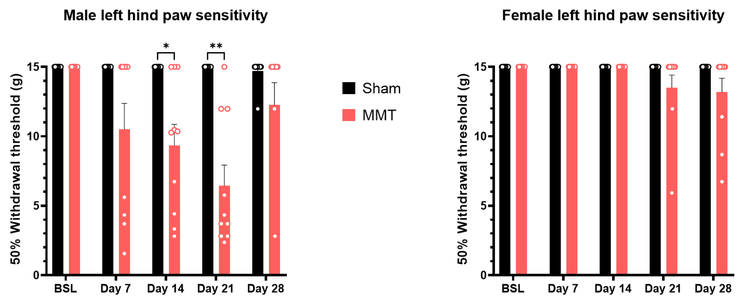
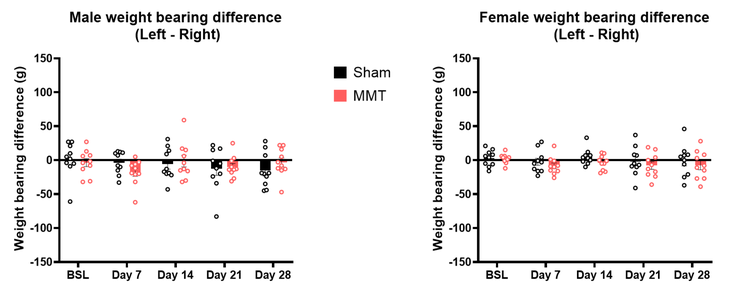
## Medial Meniscal Tear Model

### Hind paw tactile sensitivity



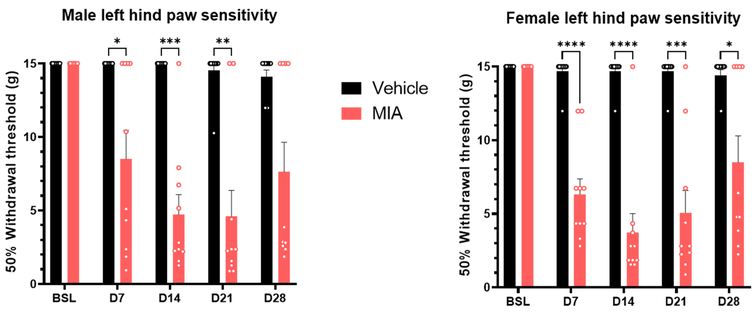

n=10/group, ** p<0.01 * p<0.05

### Dynamic weight bearing



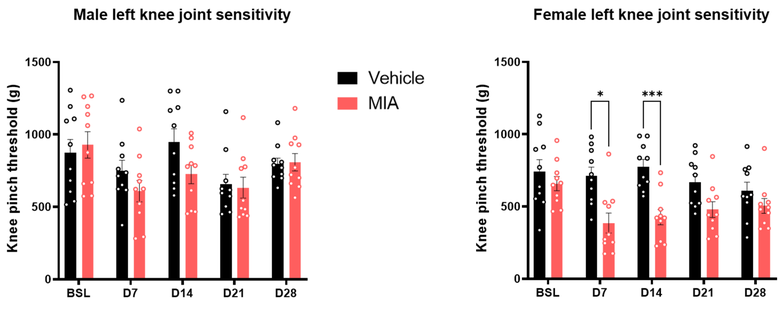

## Monoiodoacetate Model

### Hind paw tactile sensitivity



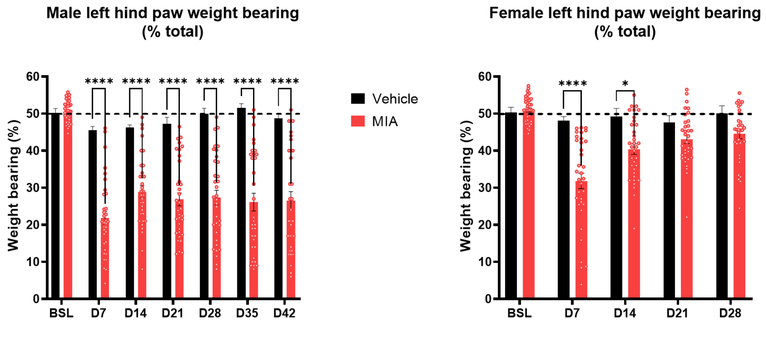

n=10/group, **** p<0.0001, *** p<0.001, ** p<0.01 * p<0.05

### Hind limb joint pressure sensitivity




n=10/group, *** p<0.001, * p<0.05

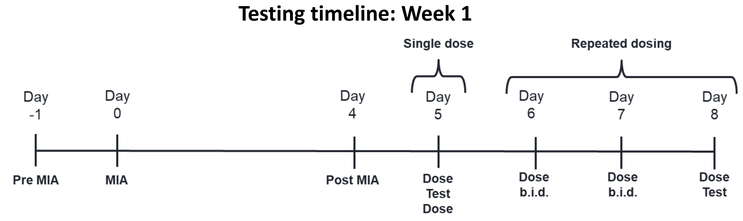
### Dynamic weight bearing



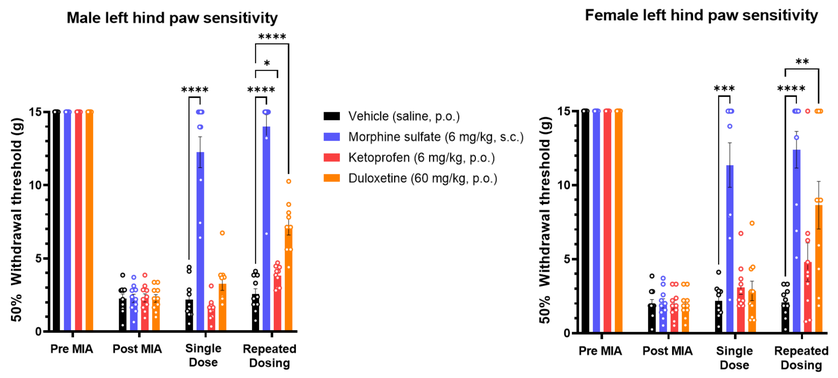

Vehicle (n=8), MIA (n=34); **** p<0.0001, * p<0.05

## Monoiodoacetate Model Pharmacology

### Testing timeline: Week 1

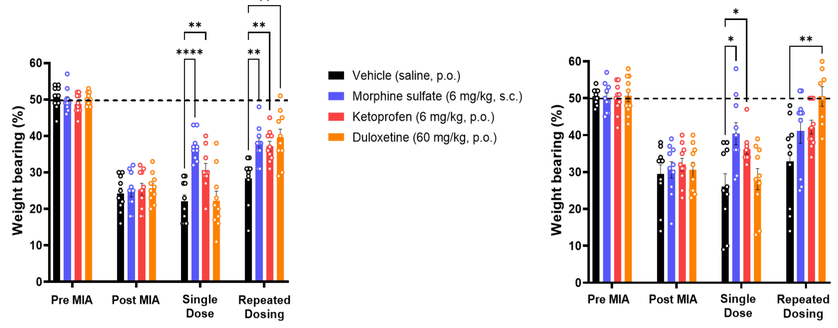



### Hind paw tactile sensitivity: Week 1



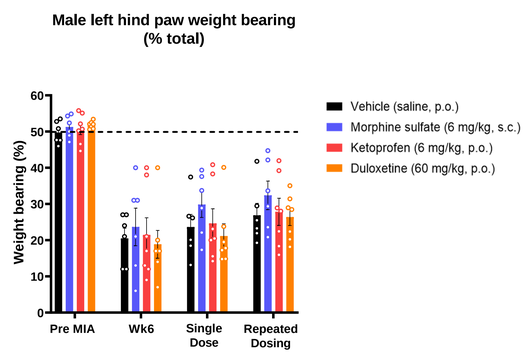

n=10/group; **** p<0.0001, *** p<0.001, ** p<0.01, * p<0.05

### Dynamic weight bearing: Week 1




n=10/group; **** p<0.0001, *** p<0.001, ** p<0.01, * p<0.05

### Dynamic weight bearing: Week 6




## Conclusion

The validation of the monoiodoacetate (MIA) model of osteoarthritis pain further highlights efforts within the NIH HEAL Initiative's PSPP program to validate clinically relevant models to evaluate novel assets to accelerate the development of novel non-opioid, non-addictive analgesics.

**PSPP is currently accepting assets for evaluation**

*For eligibility and participation inquiries, contact:*

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**For more information about PSPP, visit (or scan the QR):**
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