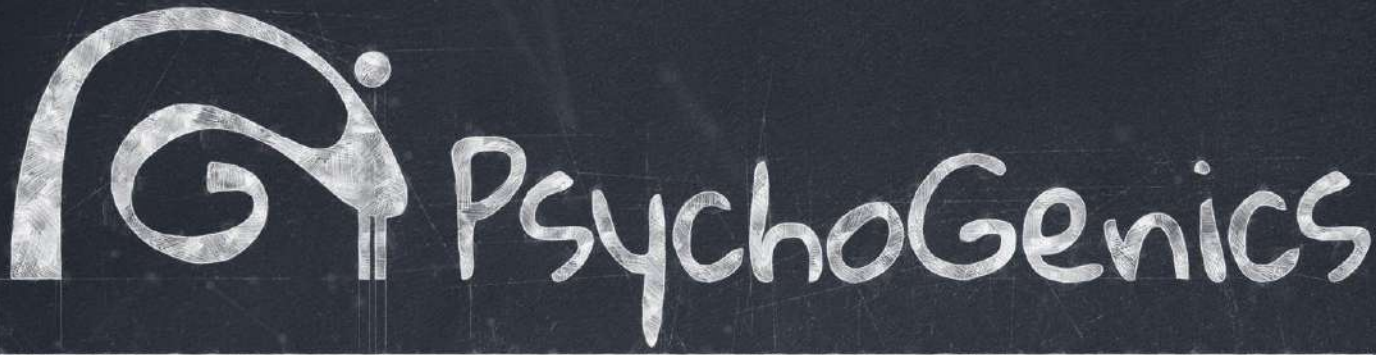
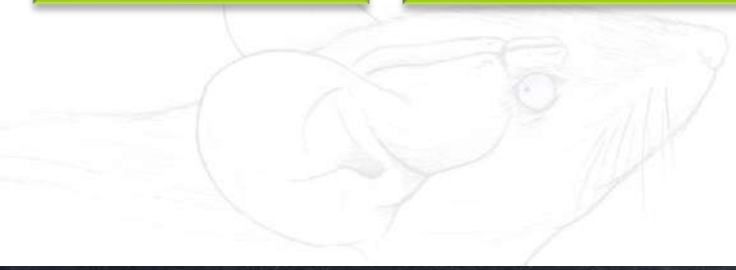


Behavior Paradigms for Pain

Pain Models at PGI

Acute	Inflammatory	Visceral Writhing	Neuropathic	Post Operative
Tail Flick Hot Plate	Formalin Carrageenan CFA ATC	Acetic Acid Phenylquinone	Chemotherapy Nerve Ligation: *Sciatic nerve* *Spinal nerve* *Spared nerve*	Brennan incisional model



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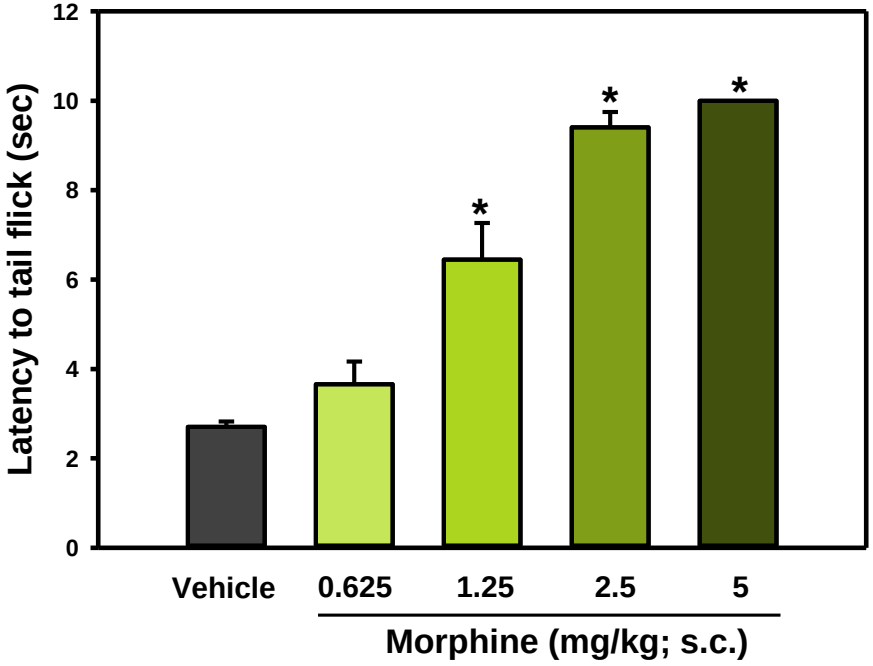
ACUTE PAIN

Tail Flick and Hot Plate

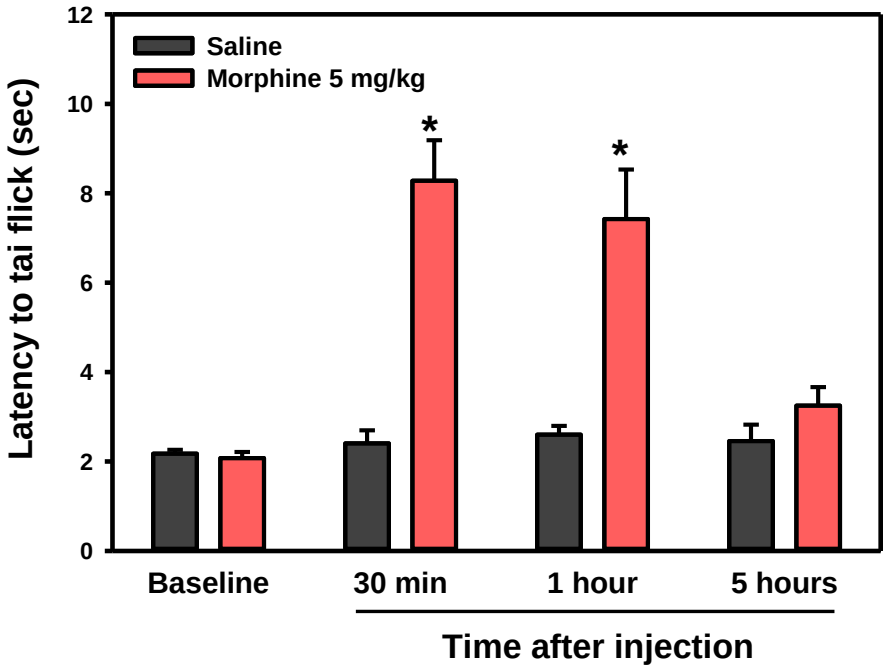
- **Tail Flick**
  - Each animal is manually restrained so that an infrared heat source is directed at a specific point on the tail
  - When the pain threshold is reached, the animal flicks its tail away from the heat source and the latency is recorded
  - The test period is limited to 10 sec to avoid tissue damage
  - An average of 3 trials is used to determine latency to pain

- **Hot Plate**
  - Each animal is placed inside an observation chamber on a hot place set to a specific temperature
  - When the pain threshold is reached, the animal respond by shaking, licking or biting their hind paws or trying to escape
  - The test period is limited to 10-60 sec (dependent on species and temperature) to avoid tissue damage

Effects of morphine on tail flick in mice

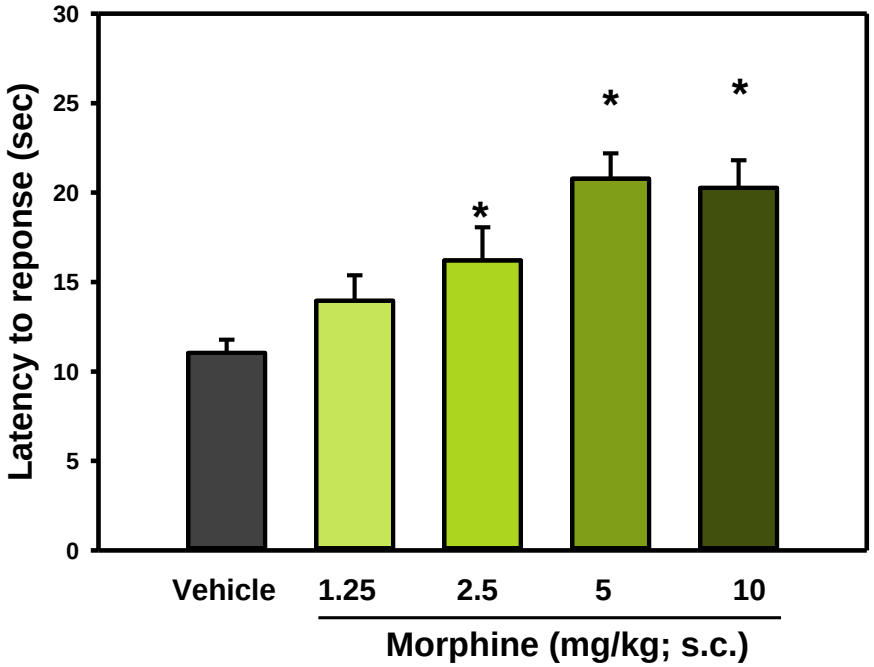


Morphine dose dependently increases the latency to tail flick in CD1 mice.

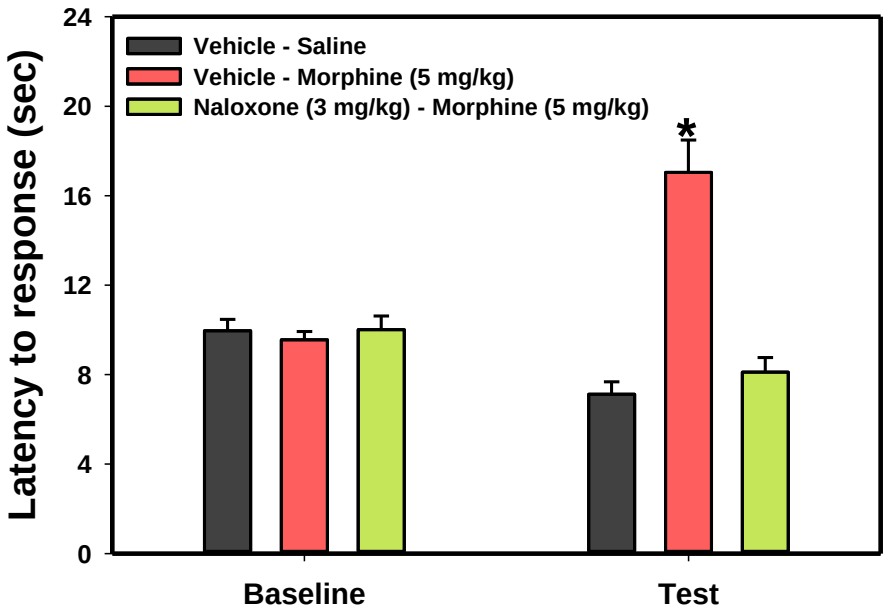


Time course for the effects of morphine in the tail flick test

Effects of morphine in the hot plate test in mice

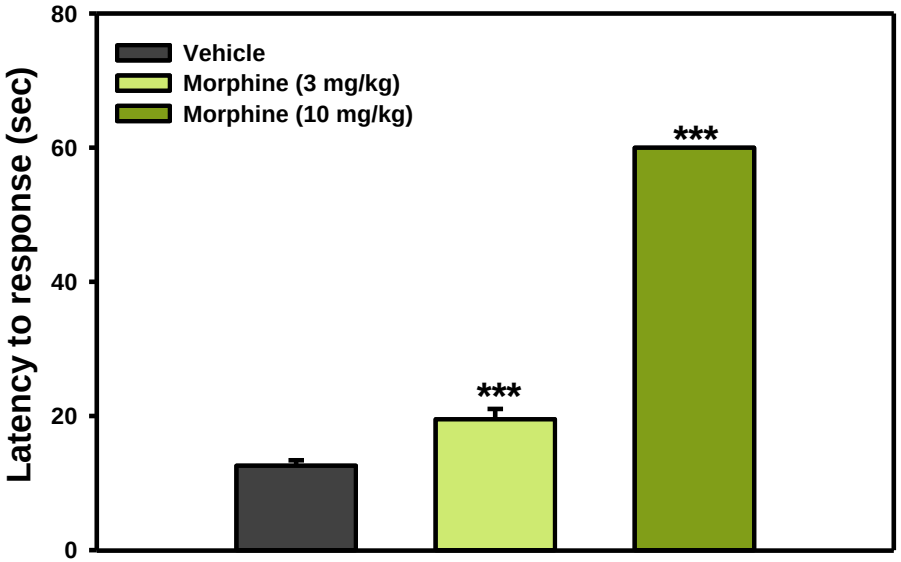


Morphine dose dependently increases the latency to paw lift from a hot plate in ICR mice.

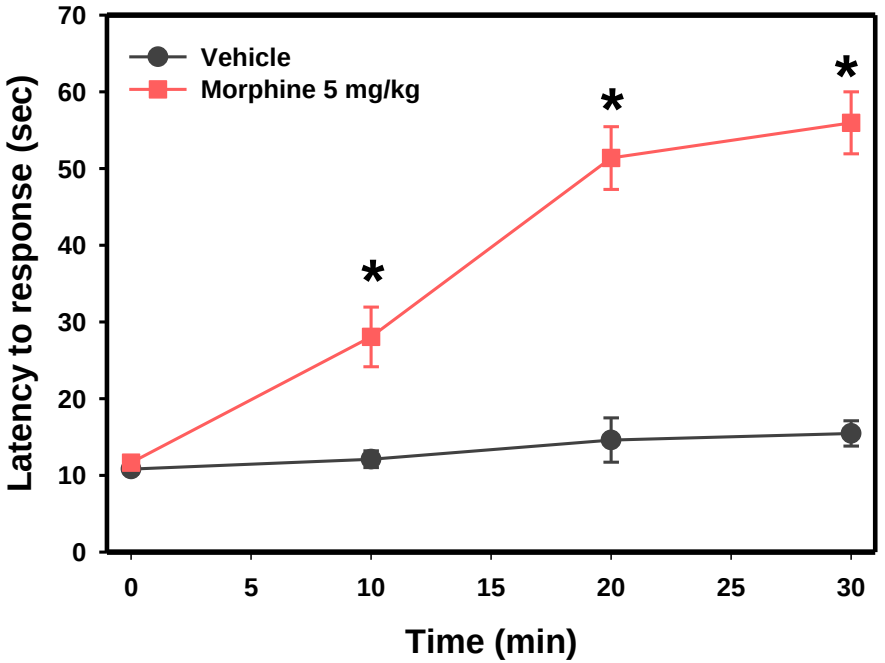


The analgesic effects of morphine can be reversed by naloxone.

Effects of morphine in the hot plate test in rats



Morphine dose dependently increases the latency to paw lift from a hot plate in SD rats.



Time course for the analgesic effects of morphine on pain response in the hot plate test in SD rats.

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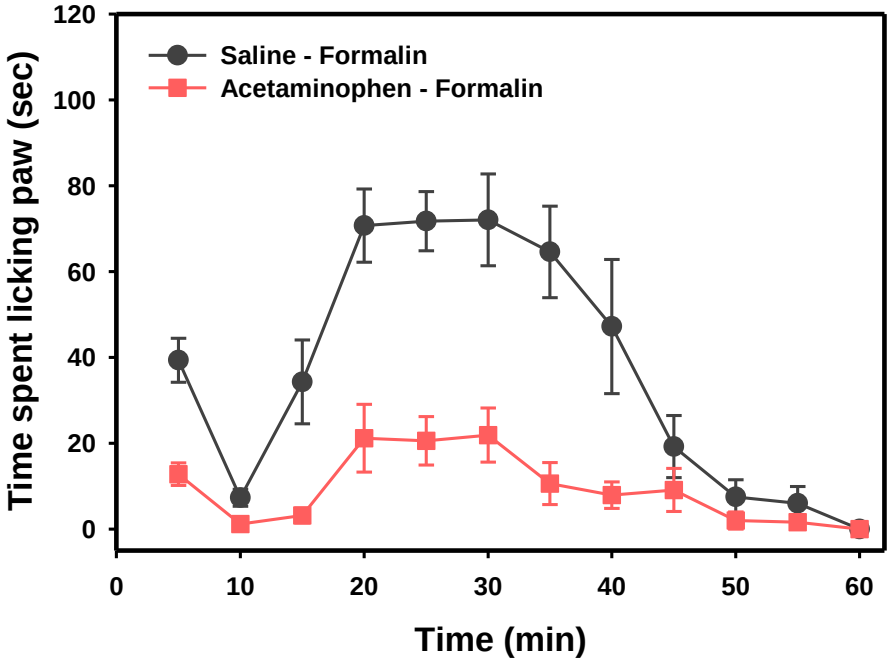
Inflammatory Pain

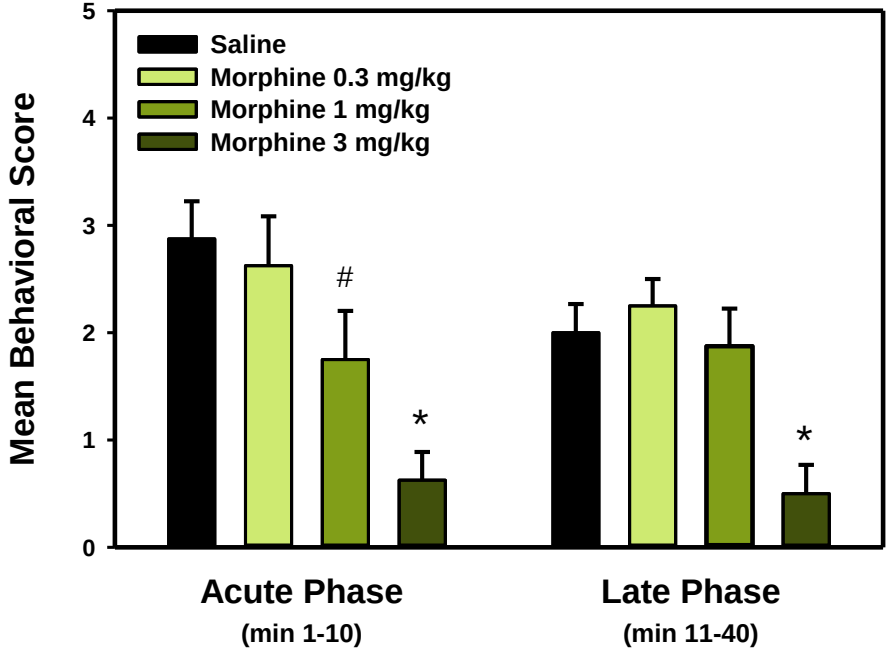
Chemical-induced inflammation

- **Formalin, carrageenan or complete Freud's Adjuvant (CFA) injected in the plantar surface of one hind paw.**
- **Two phases are seen during formalin-induced inflammation**
  - ***Phase 1: acute pain due to burst of activity from pain fibers***
  - ***Phase 2: represents responses inflammatory hyperalgesia***
- **End point measurement include**
  - **Assessment of mechanical allodynia using Von Frey Filaments**
  - **Time spent and number of behaviors (licking and biting the injected paw)**
  - **Pain Score as shown in the table below**

0: Normal weight bearing on injected paw
1: Limping or resting the injected paw lightly on the floor
2: Lifting injected paw
3: Flinching and/or shaking injected paw
4: Licking, biting or grooming injected paw

Formalin-induced inflammation in rats and mice

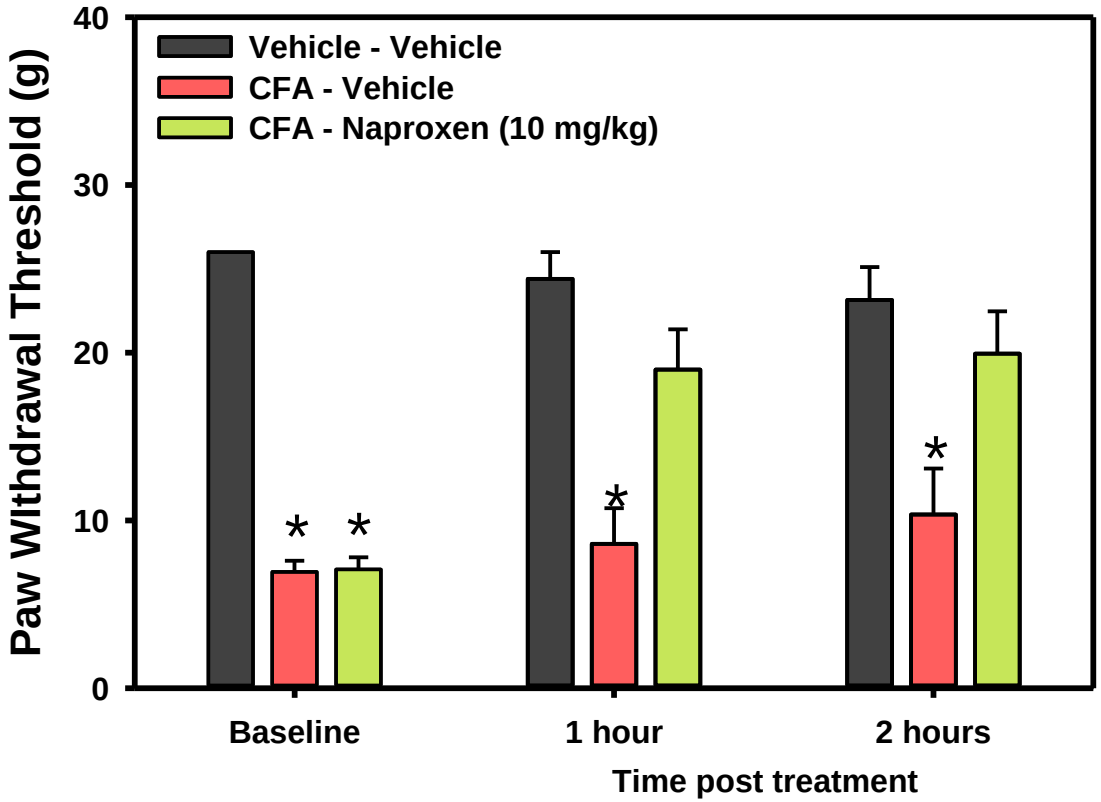




Acetaminophen attenuates formalin-induced inflammatory pain response in SD rats during early Phase and late Phase

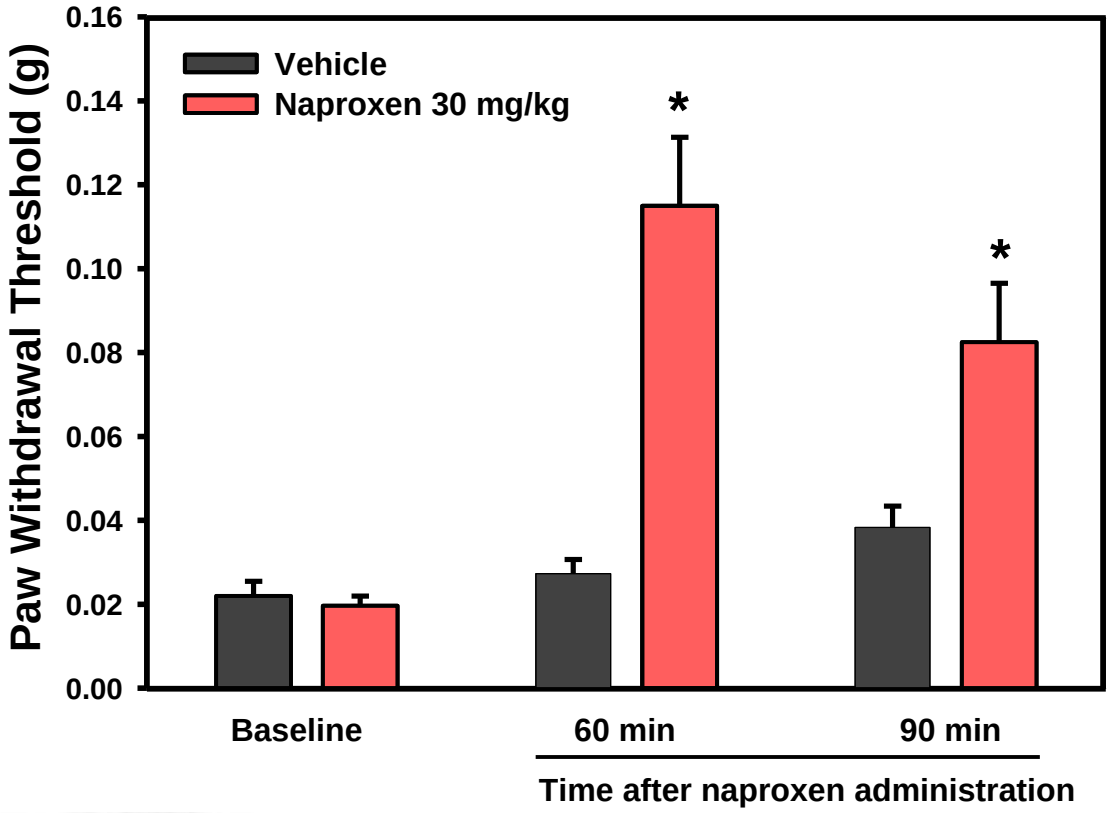
Morphine attenuates formalin-induced inflammatory pain response in C57 mice during early Phase and late Phase

CFA-induced inflammation in SD rats



Paw withdrawal threshold (PWT) was assessed using Von Frey filaments 24 hours after CFA injection. CFA decreases PWT indicative of pain response. Naproxen this pain response by increasing PWT

Carrageenan-induced inflammation in mice



Oral administration of naproxen attenuates carrageenan 25ul of 1%) pain response as seen in the increased PWT response

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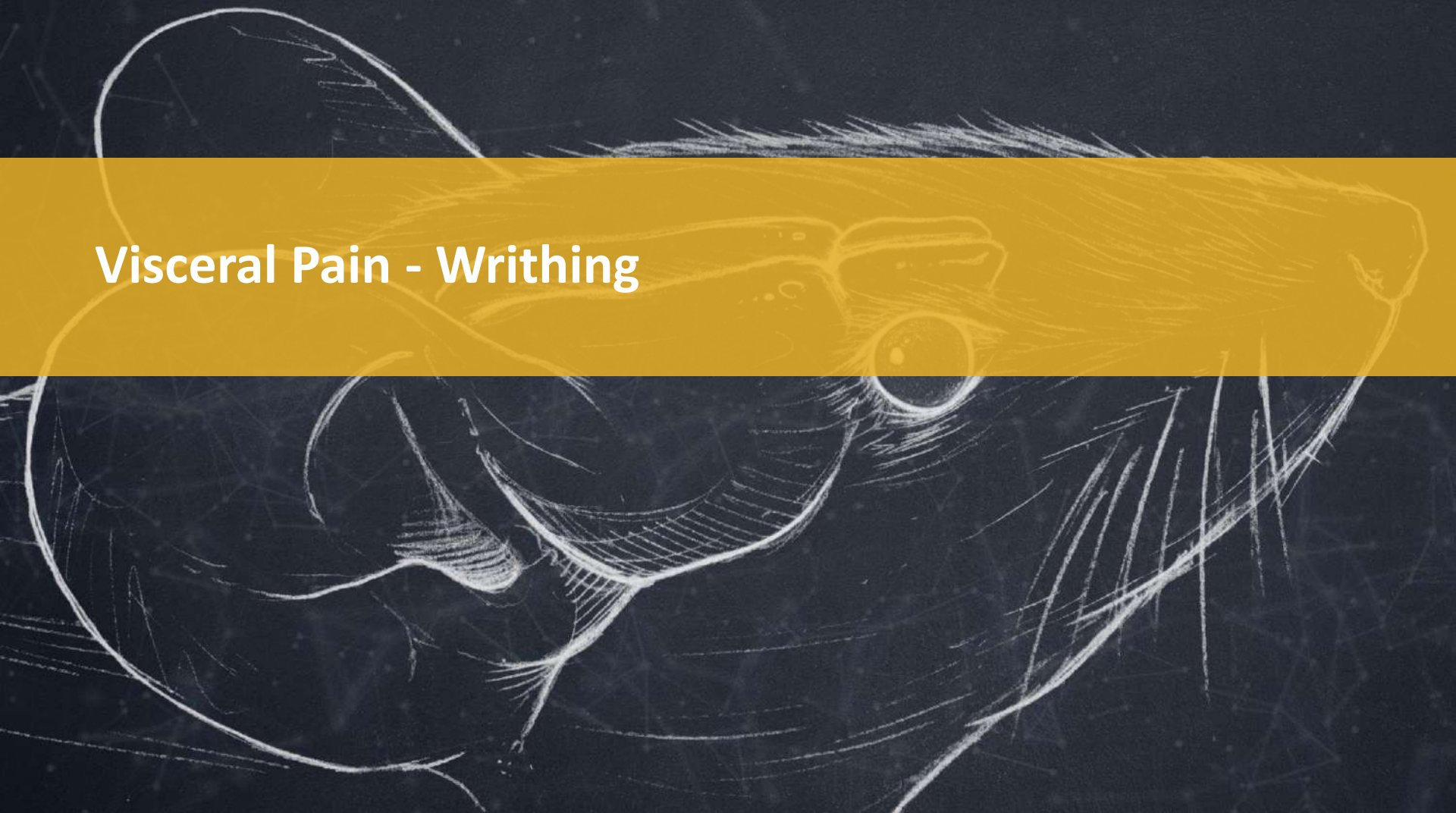
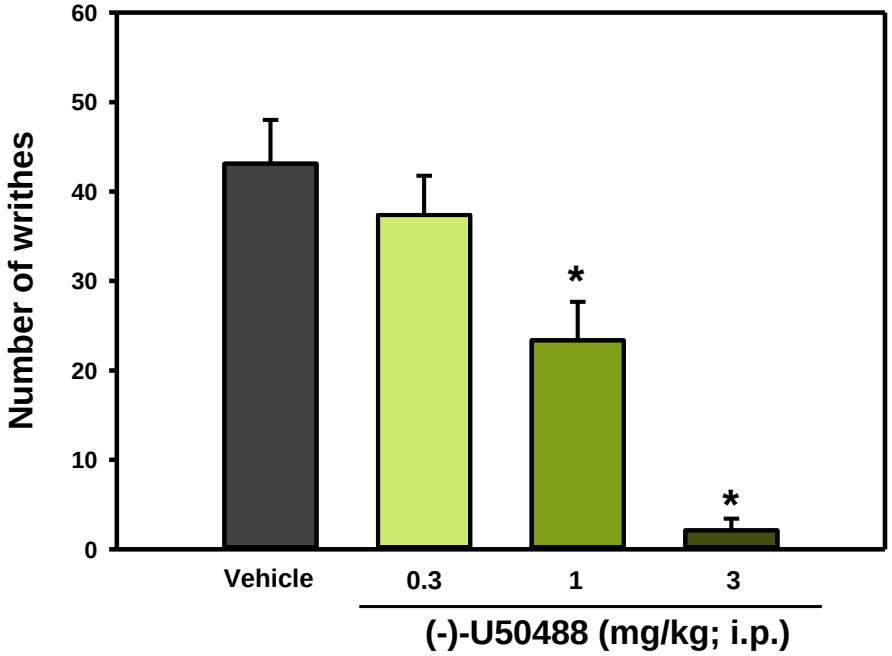
Visceral Pain - Writhing

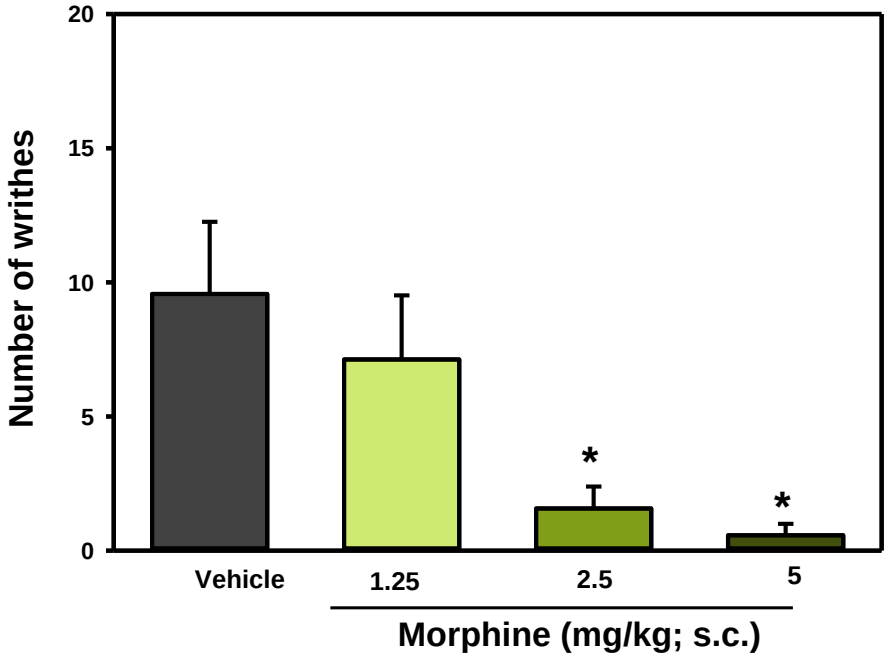


Chemical-induced writhing

- **An intraperitoneal injection of an acetic acid solution or phenylquinone induce a transient state of somatic (visceral) pain. This manifests as constriction of abdomen, turning of trunk and extension of hind legs.**
- **The number of constrictions is counted for 15 minutes**



*U50488 (kappa opioid agonist) attenuates **acetic acid** induced writhing in mice*



*Morphine attenuates **phenylquinone** induced writhing in mice*

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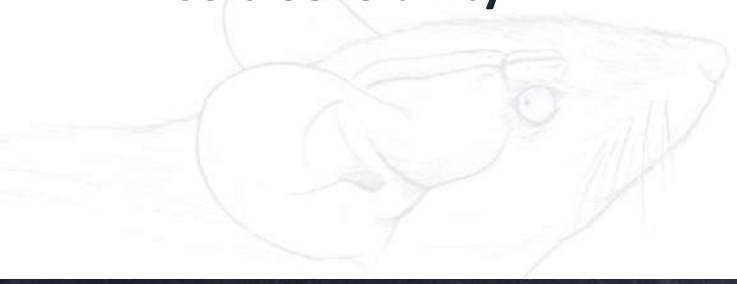
Neuropathic Pain

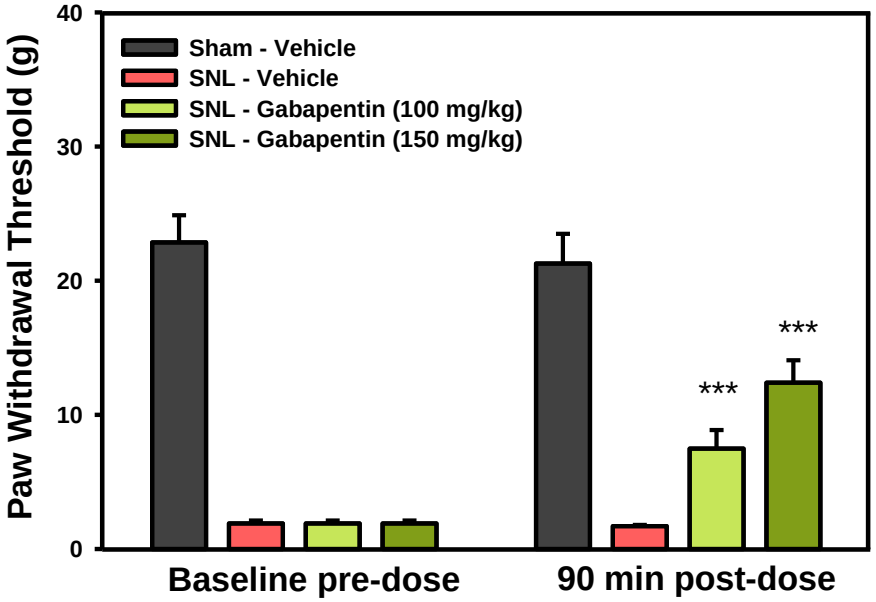
Neuropathic Pain Models

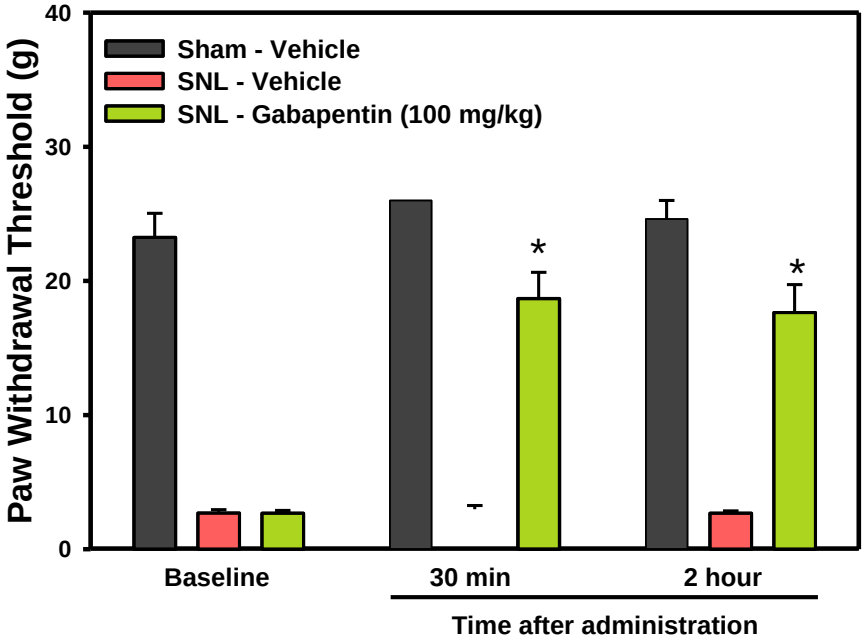
- **Nerve ligation models**
  - **Spinal (L5) nerve ligation (SNL)**
  - **Chronic constriction injury of the sciatic nerve (CCI)**
  - **Spared Nerve Injury (SNI)**
- **Chemotherapy-induced neuropathic pain**
  - **Paclitaxel**
  - **Bortezomib**
  - **Oxaliplatin**
  - **Vincristine**
- **Endpoint Measures**
  - **Evoked pain response (Von Frey)**
  - **Cold sensitivity**



Nerve Ligation Models

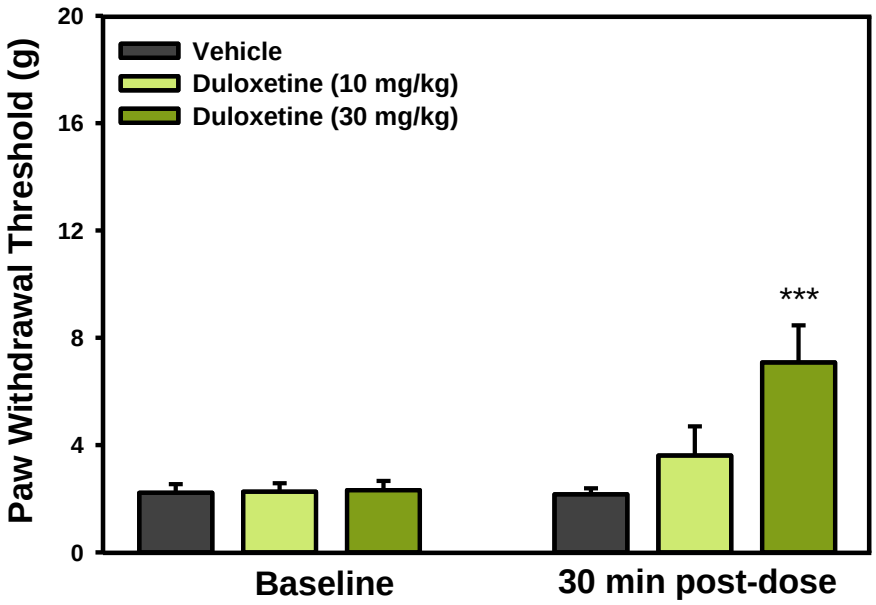
Analgesic effects of gabapentin in SNL rats

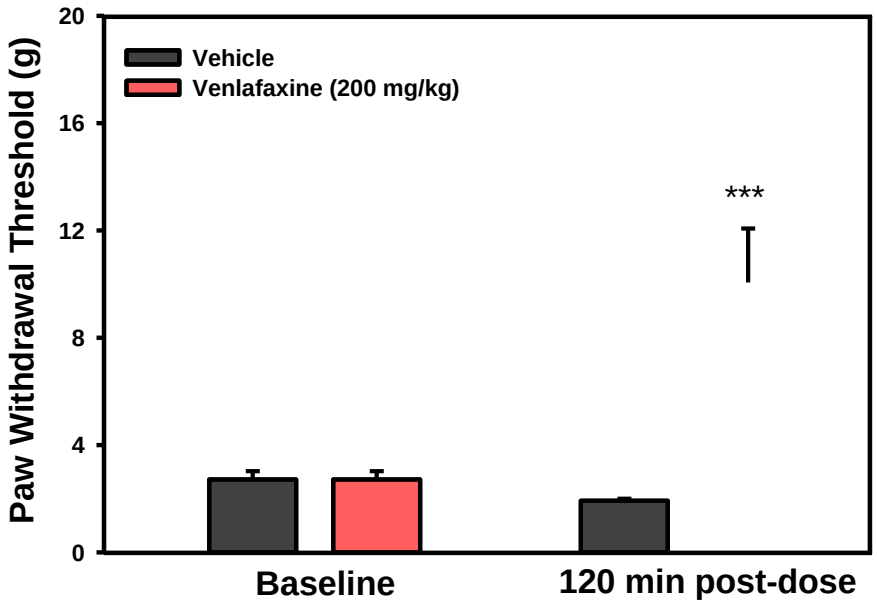




Two week post injury, SNL rats show increased pain response compared to Sham rats as seen in the decreased PWT response when measured by Von Frey filaments. Gabapentin dose dependently attenuates this pain response and increases PWT response (left). The analgesic effects of acute oral administration of gabapentin lasts for 2 hours (right).

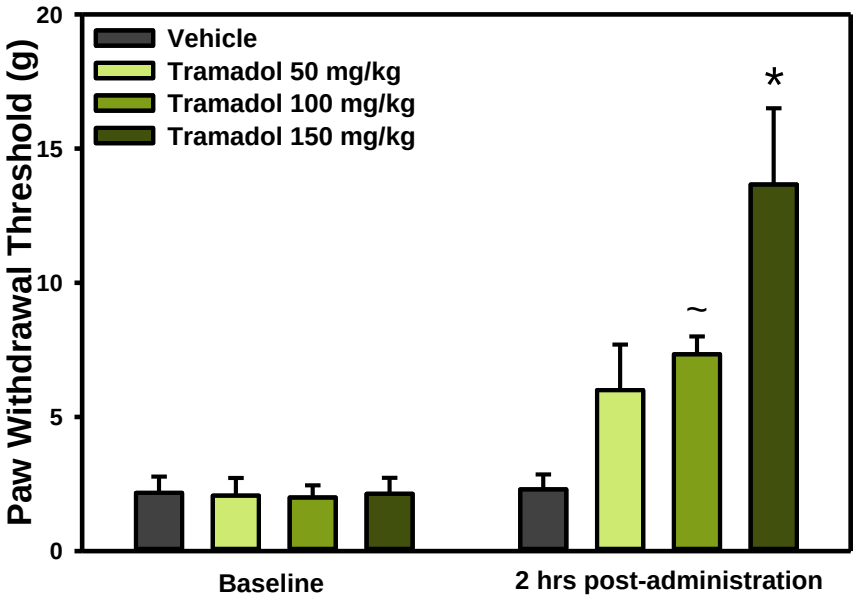
Analgesic effects of antidepressants in SNL rats

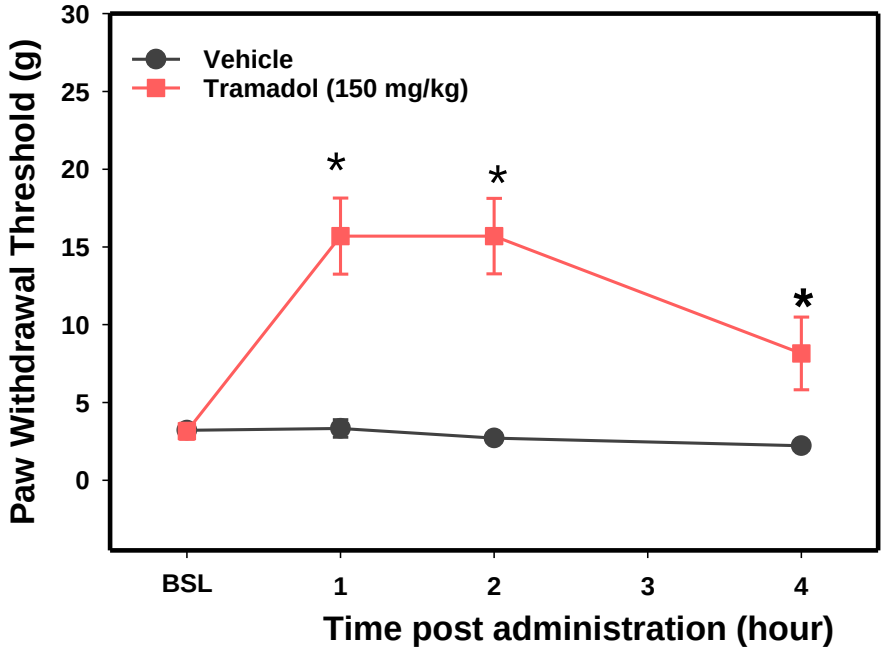




Acute oral administration of duloxetine (left) and venlafaxine (right) decreases neuropathic pain response as seen in the increased PWT response compared to vehicle-treated rats.

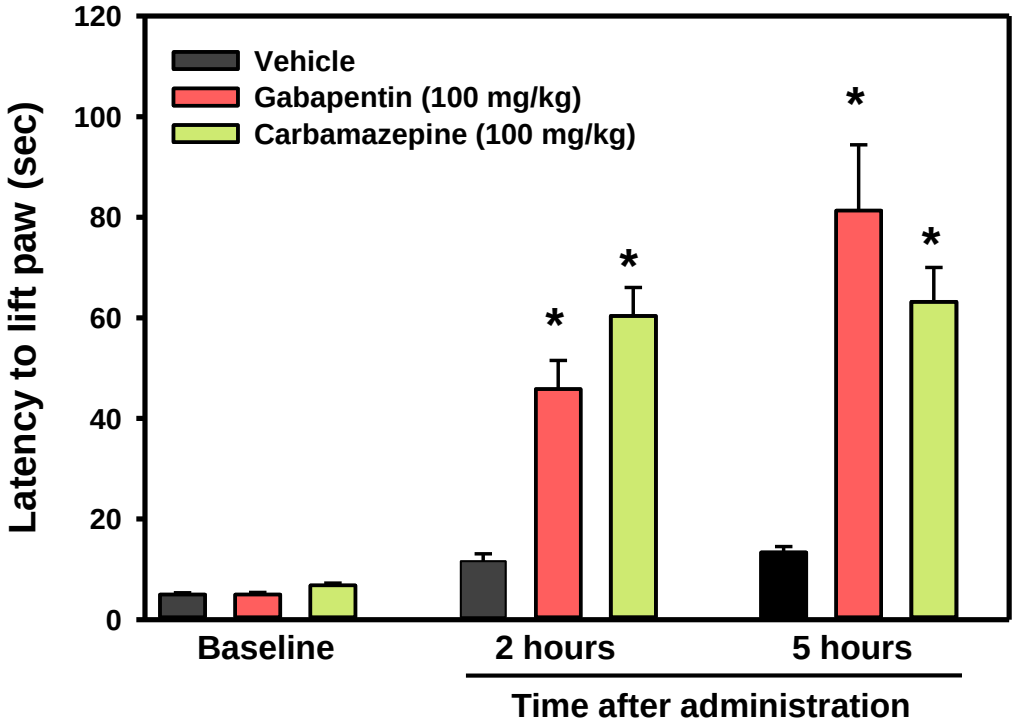
Analgesic effects of tramadol in SNL rats





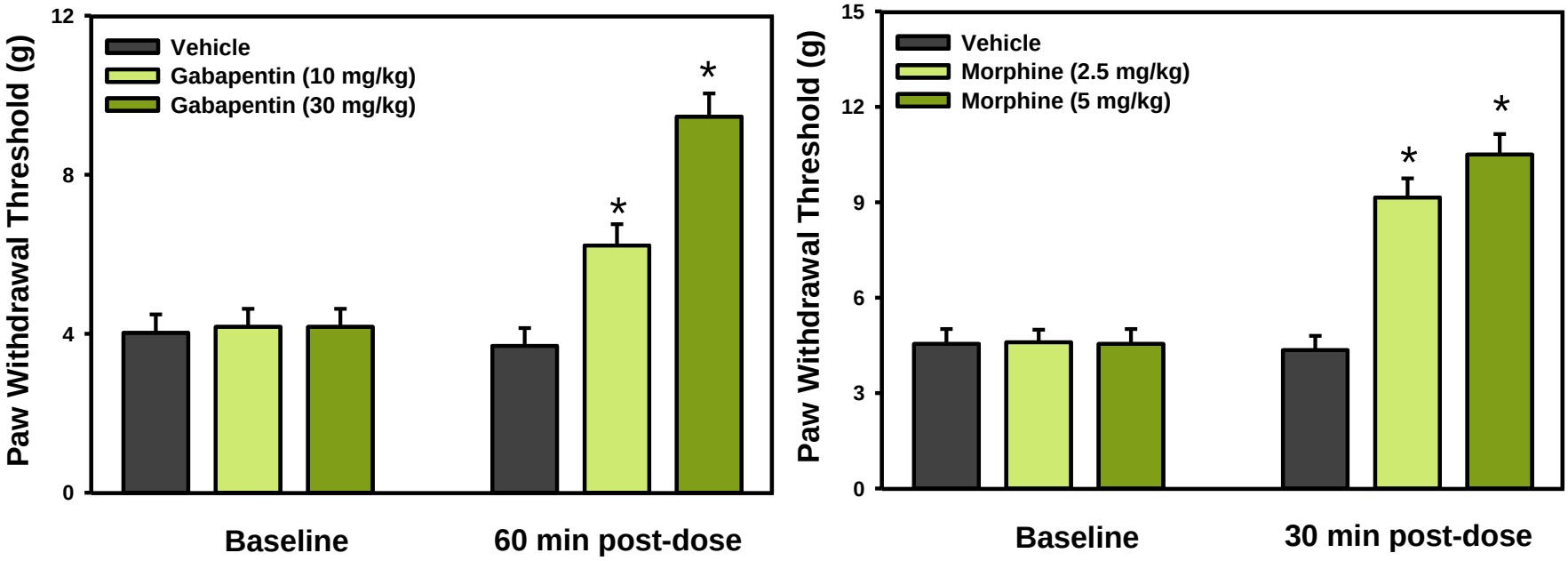
Tramadol dose dependently attenuates pain response in SNL rats and increases PWT response (left) following acute oral administration. The analgesic effects of tramadol lasts for 4 hours (right).

Analgesic effects of gabapentin and carbamazepine in CCI rats



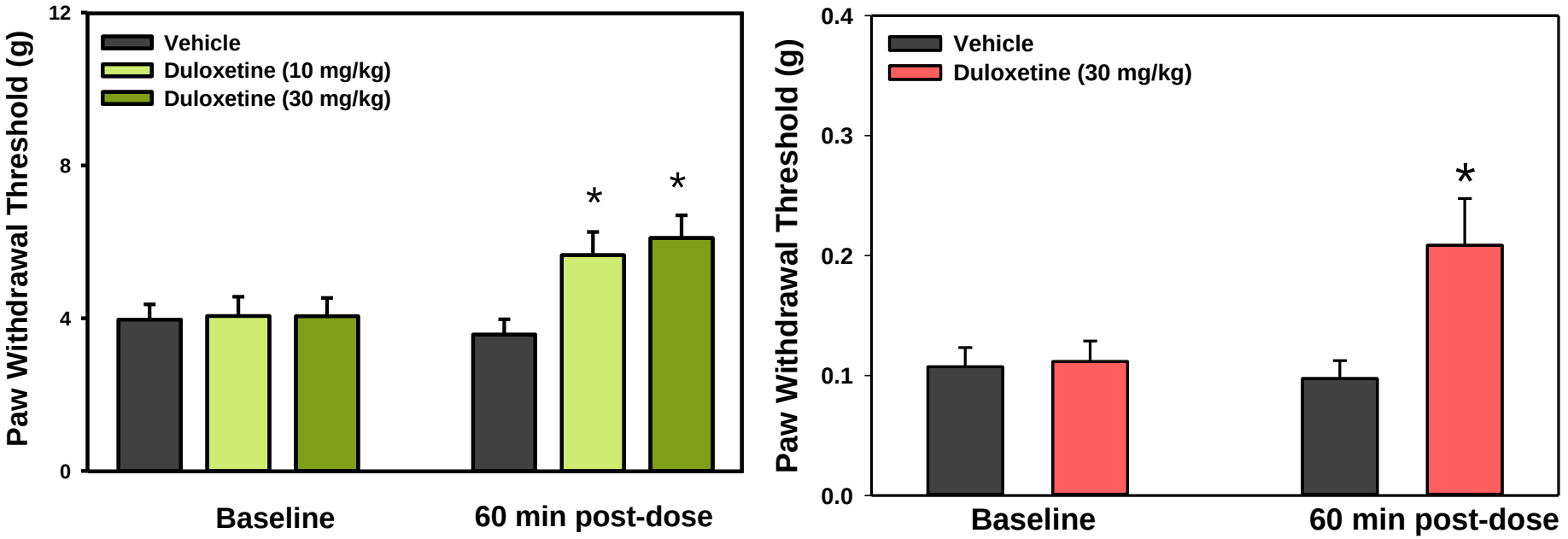
Acute oral administration of either gabapentin or carbamazepine attenuates cold allodynia as measured by the increased latency to lift the injured paw from a cold plate in CCI rats. The effect lasted 5 hours

Analgesic effects of gabapentin and morphine in CCI rats



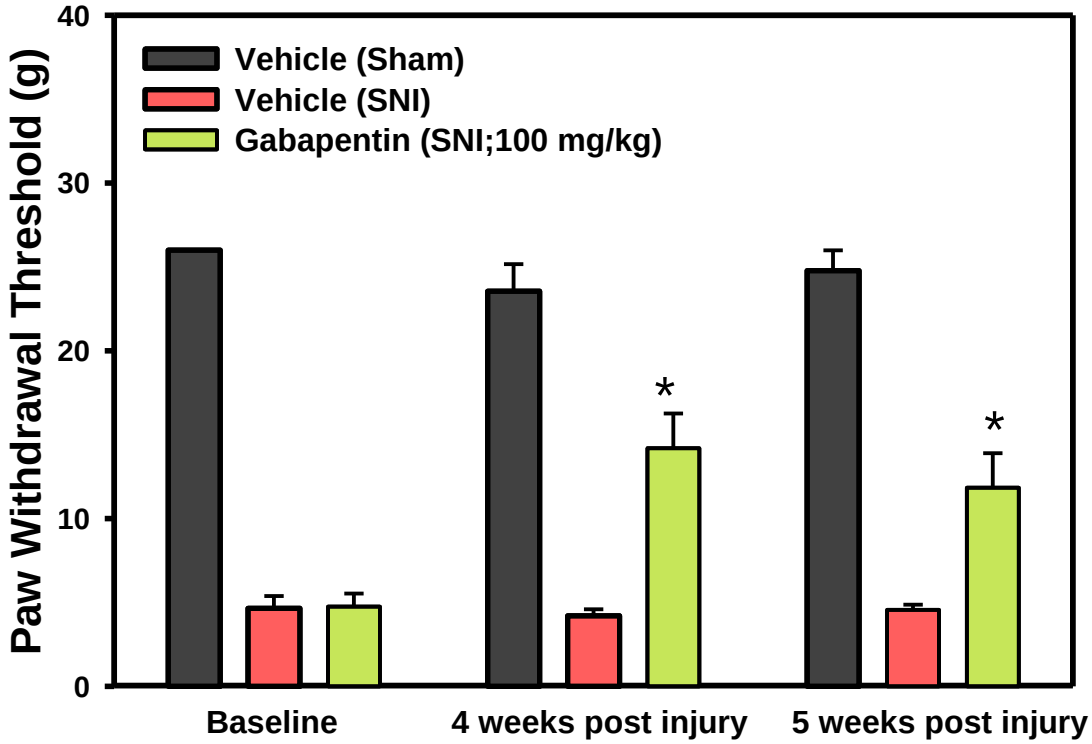
Acute administration of gabapentin (left) or morphine (right) dose dependently attenuates pain response in CCI rats two weeks post injury.

Analgesic efficacy of duloxetine in CCI rats and mice



Oral acute administration of duloxetine attenuates pain response in CCI rats (left) and CCI mice (right) and increases PWT response.

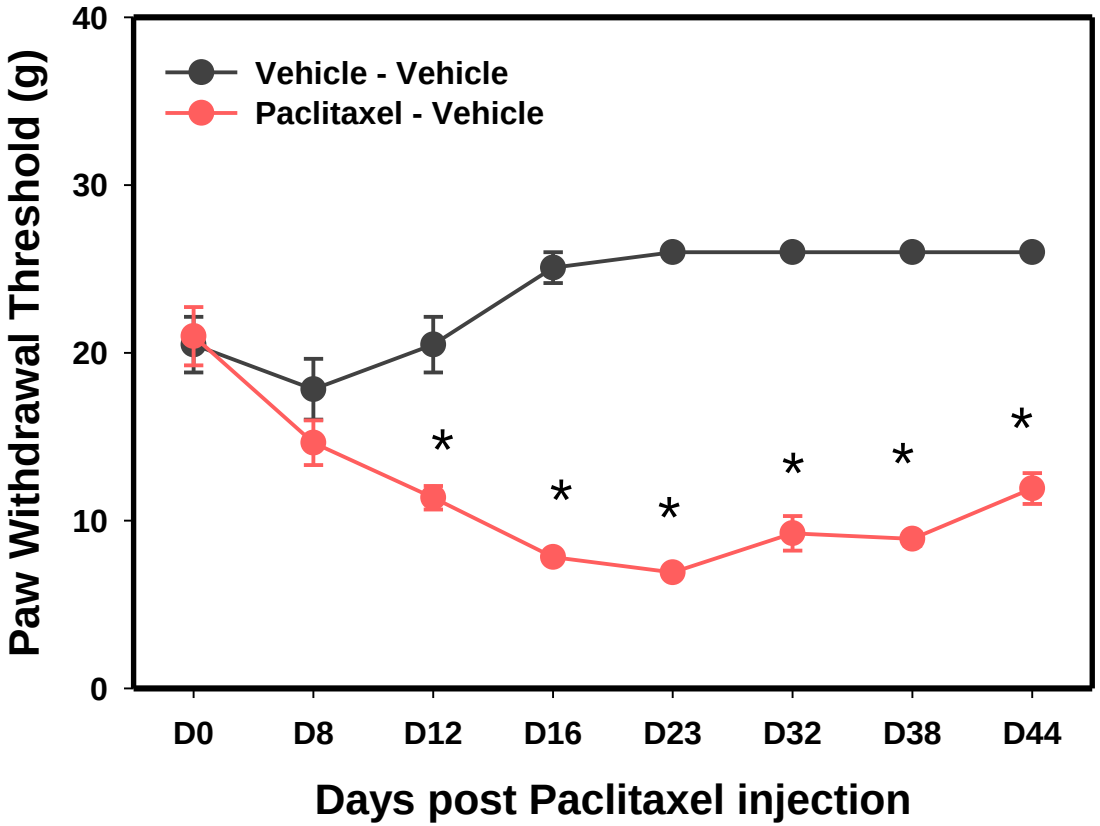
Spared Nerve Injury



Acute oral administration of Gabapentin attenuates neuropathic pain response in SNI rats as seen in the increased PWT response

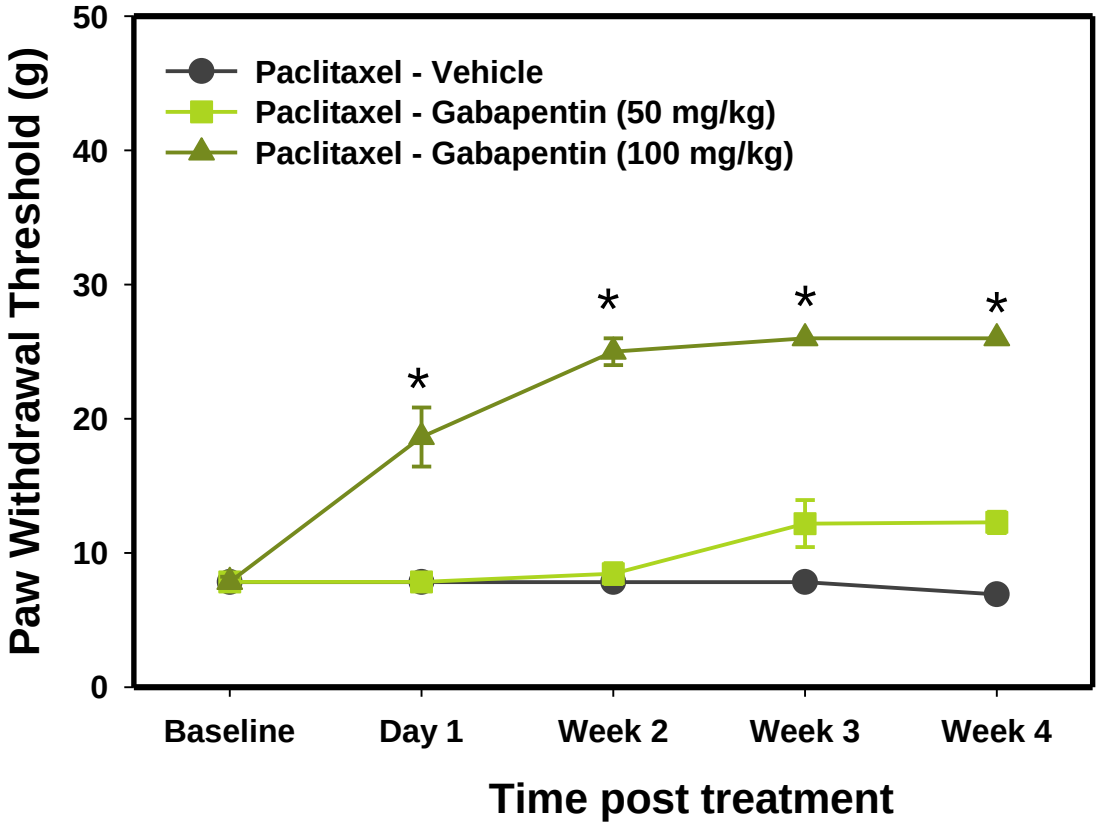
Chemotherapy- induced neuropathic pain (CINP)

Paclitaxel-induced neuropathic pain in SD rats



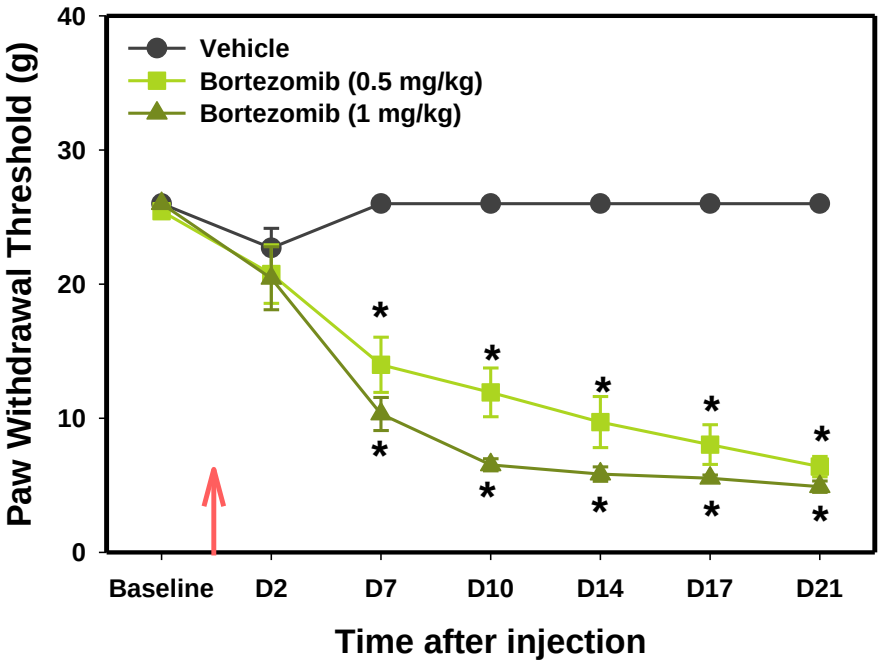
Subchronic paclitaxel injections (4 injections of 2 mg/kg QOD) induces peripheral neuropathic pain in rats. This mechanical hyperalgesia can be seen by the decrease in PWT starting from 12 until day 44

Analgesic effects of gabapentin on CINP

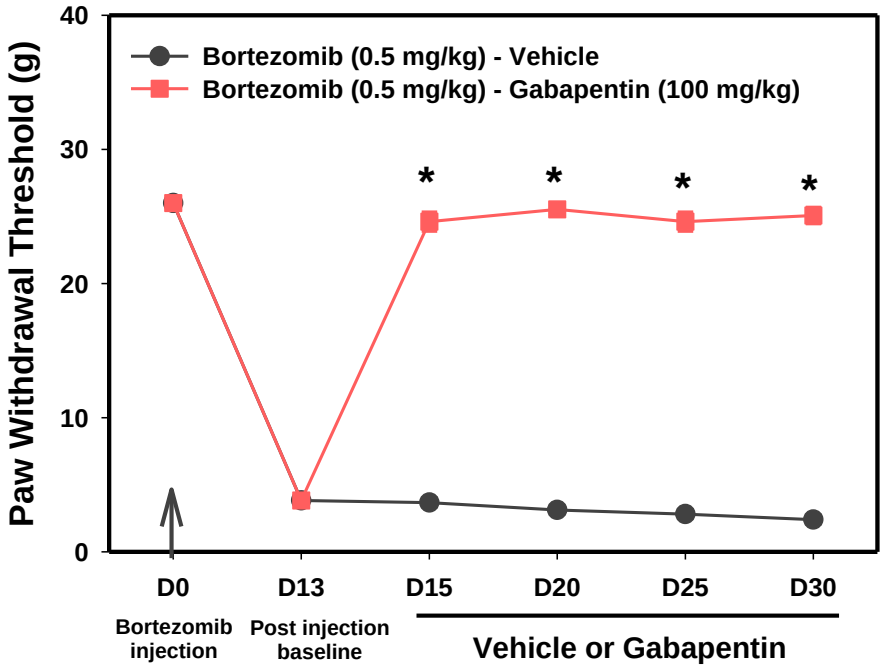


Chronic oral administration of gabapentin (100 mg/kg) attenuates neuropathic pain response in rats injected with paclitaxel as seen with the increased PWT response.

Bortezomib-induced neuropathic pain in SD rats

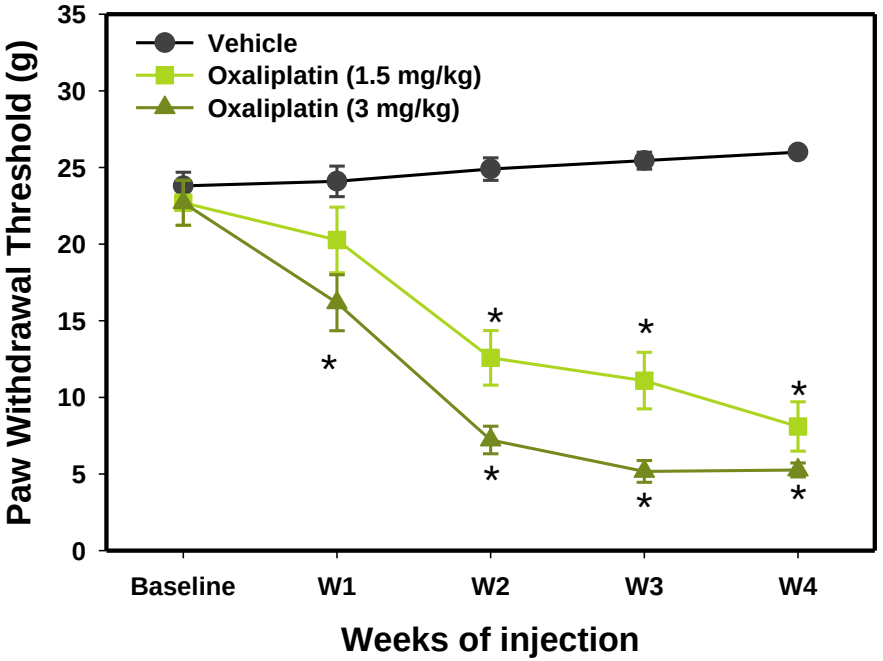


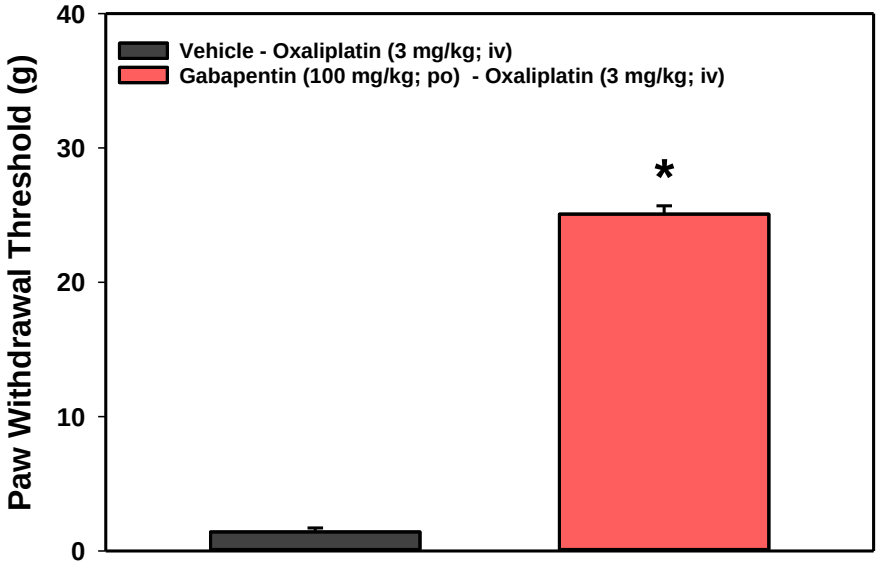
Acute injection of bortezomib (red arrow) produces long lasting neuropathic pain response as seen in the decreased PWT response compared to vehicle .



Acute injection of bortezomib (0.5 mg/kg) produced mechanical hyperalgesia that lasted for 30 days post injection. Gabapentin decreased the hyperalgesia and increased PWT of the rats compared to vehicle .

Oxaliplatin and vincristine-induced neuropathic pain in SD rats

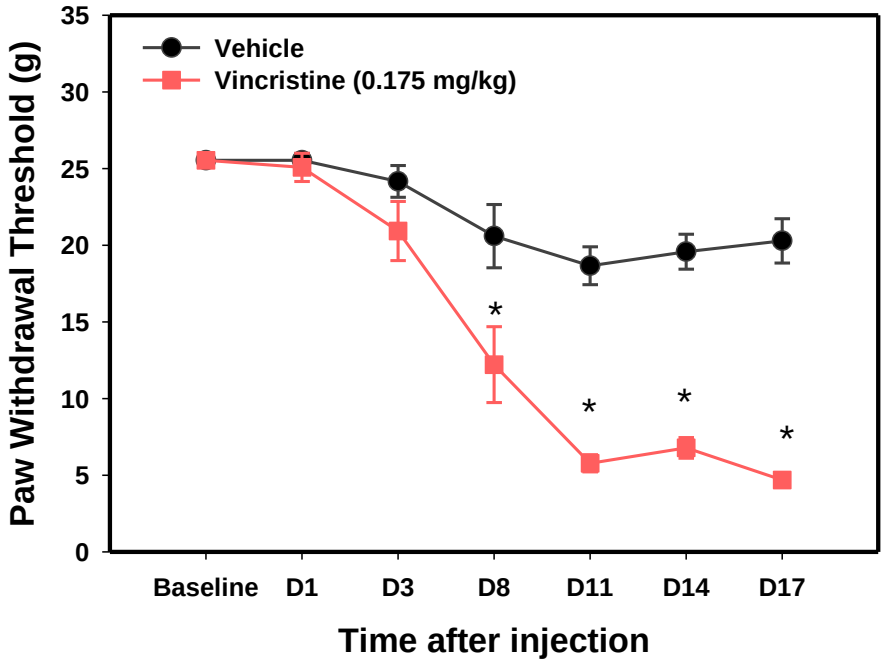




Intravenous injection of oxaliplatin (twice weekly) dose dependently induces peripheral neuropathic pain in rats and decreases PWT response.

Gabapentin (100 mg/kg; po) increases PWT during week 4 of oxaliplatin treatment.

Vincristine-induced neuropathic pain in SD rats



Intravenous injection of vincristine (QOD for a total of 5 injections) induces mechanical hyperalgesia as seen in the decreased PWT response.

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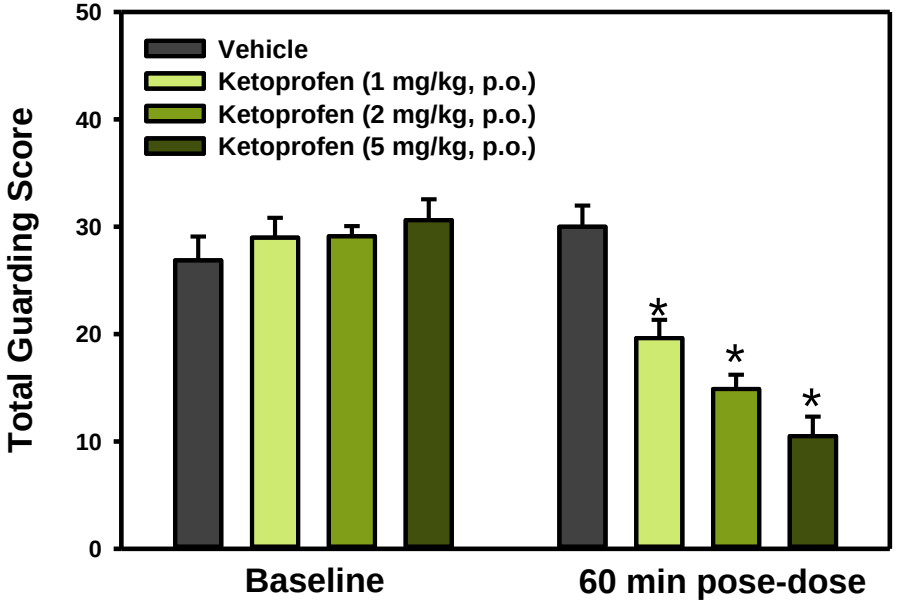
Incisional Pain

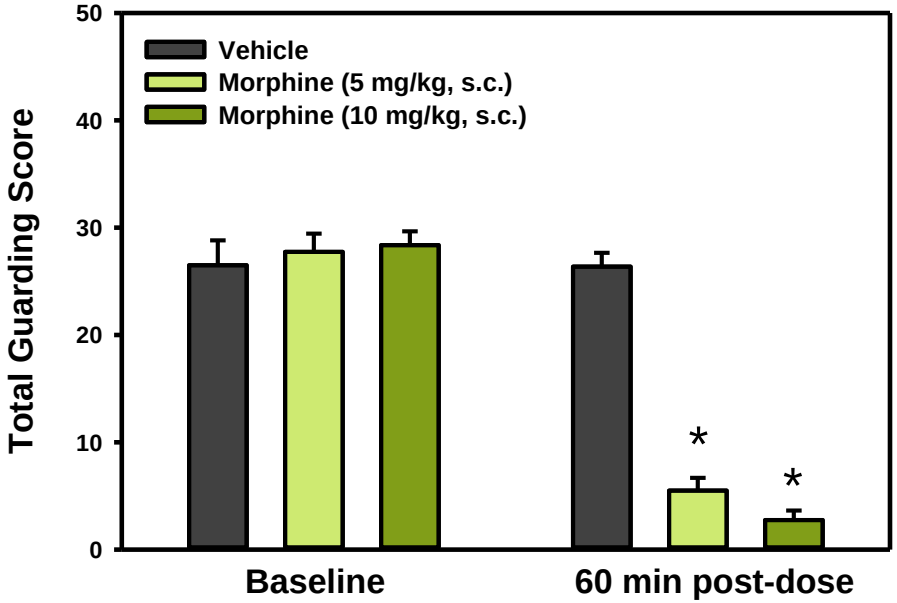
Brennan model of incisional pain

- **Postoperative pain is a common form of acute pain for which effective treatments are not yet available.**
  - Treatment of persistent or chronic pain can be hindered by the limited efficacy and side effects of currently available analgesics (e.g., opioids or anti-inflammatory drugs).
- **Pain behaviors are greated immediately after recovery from anesthesia and can persist for several days** (*Peters and Eisenach, 2010; Obata, 2010).*
- **Operative pain in humans can be mimicked by paw incision in rats** *(Brennan, et al., 1995; Kang et al., 2010). Rats are assessed based on guarding scores:*

0: plantar surface, toes, and heel of ipsilateral paw are firmly on mesh floor, balancing weight uniformly with contralateral paw.
1: ipsilateral heel is raised, but the animal is still bearing some weight on the plantar surface and toes. At this stage, the distribution of weight between the ipsilateral and contralateral paws ceases to be equal, and signs of blanching, or whitening, of the ipsilateral paw should be a sign of such a case
2: ipsilateral paw is not bearing weight (may be flat and held out to the side) or the animal is only on its toes. Heel, and possibly plantar surface and base of the toes may be raised up, but not totally away from the mesh floor, with an unbalanced support of weight
3: ipsilateral paw is lifted up completely and being held close to the body.

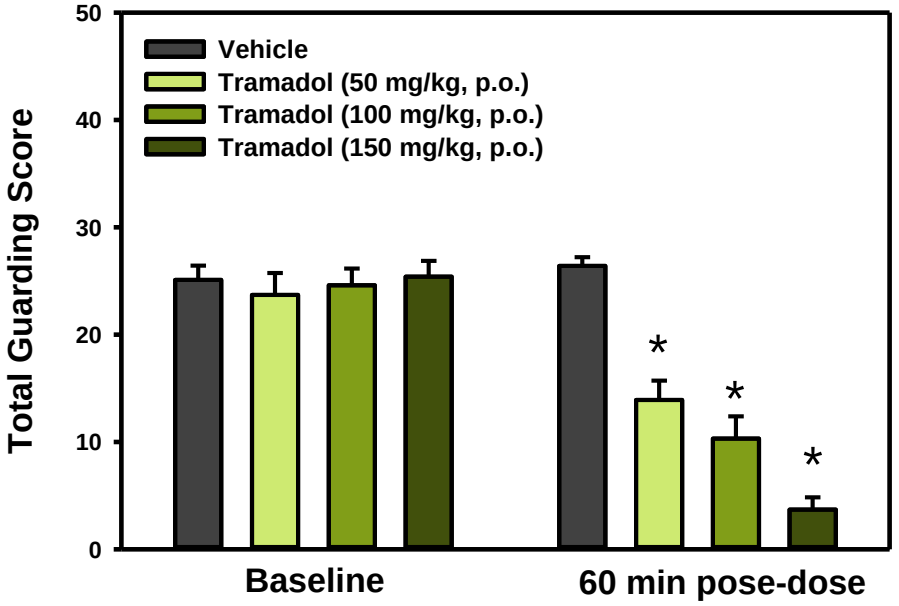
Analgesic effects of ketoprofen and morphine

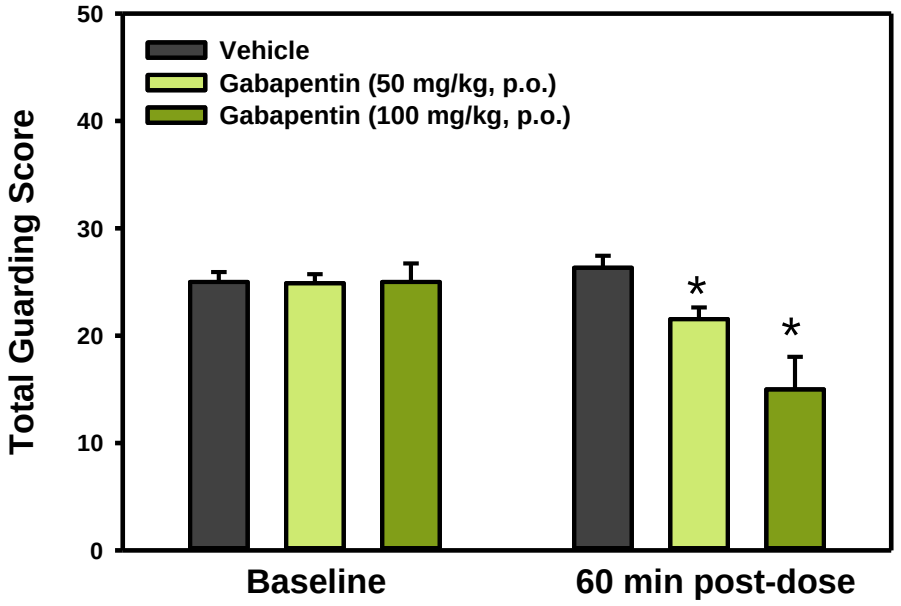




Acute administration of either the NSAID ketoprofen (left) or morphine (right) 1 hour post surgery decreases guarding scores in SD rats in a dose dependent manner.

Analgesic effects of gabapentin and tramadol





Acute oral administration of either tramadol (left) or gabapentin (right) dose dependently decreases guarding scores when administered 1 hour post surgery.