Update on Pain Management

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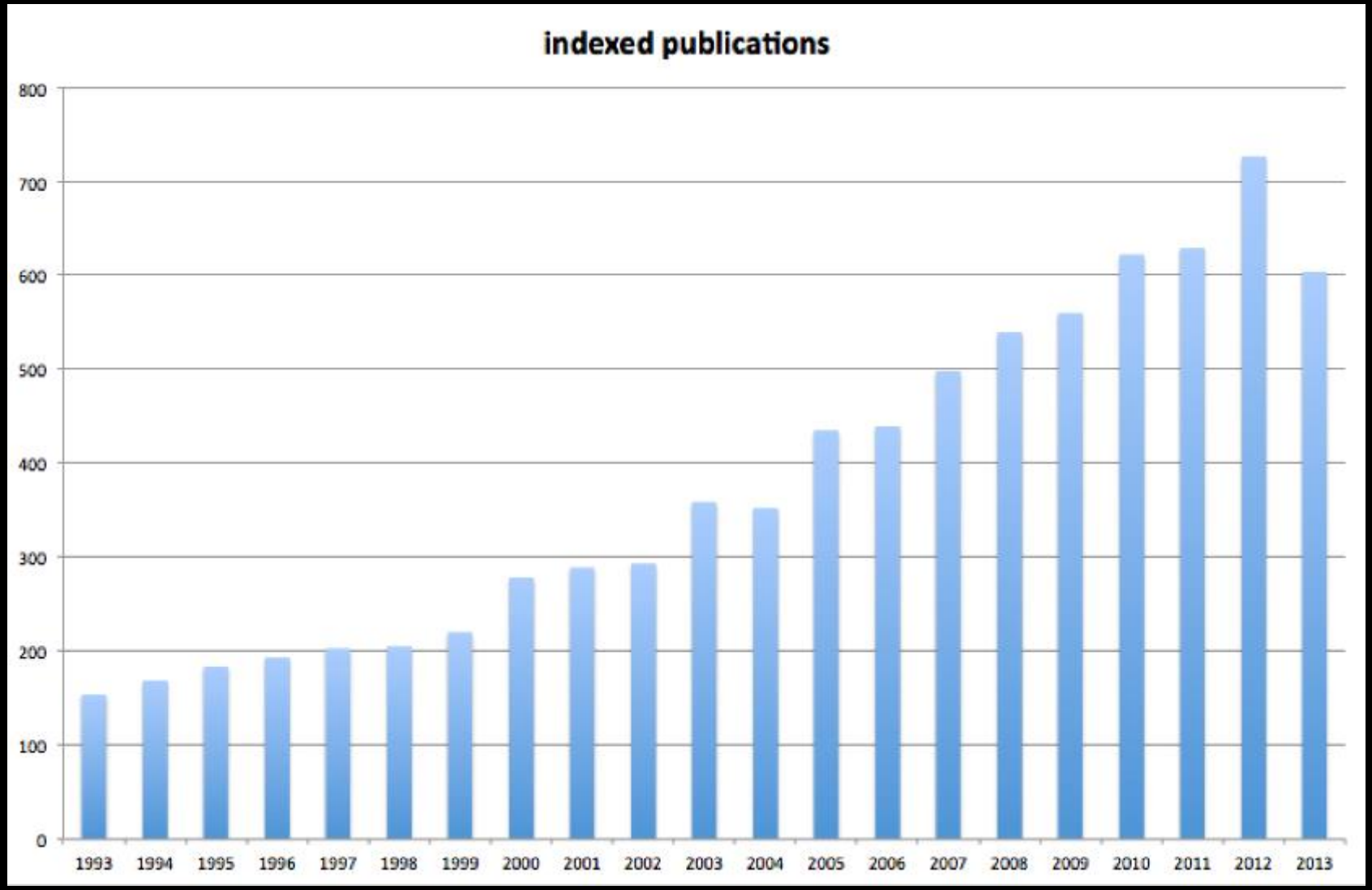
Rising number of publications indexed on Pubmed with keywords “analgesia” or “pain” and “laboratory animals.”



Tile of Talk: Special Topic Lecture: Update on Pain Management
Presenter: Jennifer Lofgren, DVM, MS, DACLAM

Objective Statement: The objective of this talk is to provide the participants with an overview of recent advancements in the prevention and treatment of pain in laboratory animal species. This talk will review different approaches to pain management, taking into account ease of delivery in a high throughput setting.

Abstract: Providing effective analgesia is an ever-present challenge to laboratory animal veterinary staff. Recent evaluations of novel analgesics, sustained release and oral formulations, multimodal analgesic combinations, and even non-pharmacological approaches to preventing, minimizing, and treating pain in lab animal species may provide new tools for the lab animal veterinarian's toolbox.

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Sustained Release Analgesia:

Publication	Dose	Summary
Chum, 2014	0.3, 1.2, or 4.5 mg/kg SC BupSR (ZooPharm) (Rats)	Marked sedation and weight loss observed with 4.5 mg/kg. BupSR at 0.3 or 1.2 mg/kg SC was effective in minimizing hypersensitivity with minimal sedation for at least 48 h, possibly 72 h. BupSR appeared to be as efficacious as BID dosing of Bup-HCl.
Nunamaker, 2013	0.2 mg/kg SC BupSR (ZooPharm) (Macaque)	Similarity in buprenorphine metabolism between dogs and macaques. Dogs have an analgesic plasma threshold of 0.1 ng/mL buprenorphine. Therefore as the macaques reached plasma buprenorphine levels greater than 0.1 ng/mL the BupSR was likely therapeutic. Authors recommend: (1) Bup-HCl at 0.01 mg/kg IM should be administered every 6 to 8 h; (2) Bup-HCl at 0.03 mg/kg IM should be administered every 12 h; and (3) 0.2 mg/kg SC BupSR should be administered once every 5 days.
Foley, 2011	1.2 mg/kg sustained-release formulation BupSR (ZooPharm) (Rats)	BupSR increased latency to withdrawal from thermal stimuli and equivalent number of rears after tibial surgery as non-surgical controls. BupSR appeared to be analgesic for 2-3 days. Plasma concentrations remained over 1 ng/mL for 72 h after a single dose of BupSR (0.9 mg/kg).
Carbone, 2011	1.0 mg/kg BupSR (ZooPharm) (Mice)	BupSR increased thermal latency for 2, 6, and 12 h compared with saline. Majority of mice developed scabs at site of injection; possibly because the solution was viscous and the inability to dilute required injection of a small concentrated volume.
Catbagan, 2011	0.12 mg/kg BupSR (ZooPharm) (Cats)	For post-OVH pain, BupSR had comparable efficacy and adverse effect profile as that of twice-daily oral transmucosal administration of Bup-HCl before and after surgery.

Sustained Release Analgesia References:

1: Chum HH, Jampachairsri K, McKeon GP, Yeomans DC, Pacharinsak C, Felt SA. Antinociceptive effects of sustained-release buprenorphine in a model of incisional pain in rats (Rattus norvegicus). *J Am Assoc Lab Anim Sci.* 2014 Mar;53(2):193-7.

2: Nunamaker EA, Halliday LC, Moody DE, Fang WB, Lindeblad M, Fortman JD. Pharmacokinetics of 2 formulations of buprenorphine in macaques (*Macaca mulatta* and *Macaca fascicularis*). *J Am Assoc Lab Anim Sci.* 2013 Jan;52(1):48-56.

3: Carbone ET, Lindstrom KE, Diep S, Carbone L. Duration of action of sustained-release buprenorphine in 2 strains of mice. *J Am Assoc Lab Anim Sci.* 2012 Nov;51(6):815-9.

4: Catbagan DL, Quimby JM, Mama KR, Rychel JK, Mich PM. Comparison of the efficacy and adverse effects of sustained-release buprenorphine hydrochloride following subcutaneous administration and buprenorphine hydrochloride following oral transmucosal administration in cats undergoing ovariohysterectomy. *Am J Vet Res.* 2011 Apr;72(4):461-6.

5: Foley PL, Liang H, Crichlow AR. Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats. *J Am Assoc Lab Anim Sci.* 2011 Mar;50(2):198-204.

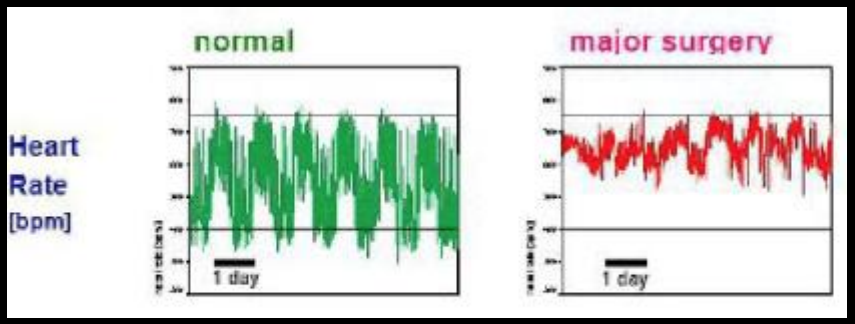
Hot Topics in Analgesia

- Pain Assessment
- Non-pharmacologic Analgesia
- Oral Dosing of Analgesia
- Sustained Release Analgesia
- Tramadol
- Multimodal Analgesia
- Transdermal Analgesia
- Regional Analgesia

Pain Assessment

Facial Coding Unit	Score
Orbital Tightening	2
Cheek Flattening	1
Pointed Nose	2
Whisker Change	2
Total Pain Score:	2

b.



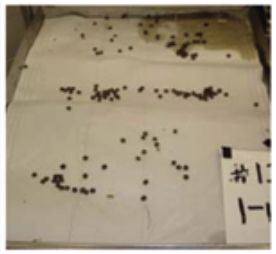
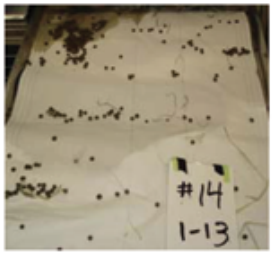
SCORE	DESCRIPTION	PHOTO IDEAL
0	Fewer than 20-40 droppings. Poorly formed feces, usually tiny and distorted in shape (oval).	

Identifying Pain

- Consumption behaviors / Body Weight
- Fecal or Serum Corticosterone
- Telemetry
- Pain Specific Behaviors
- Pain Faces
- Nesting

Consumption/Body Weight

- After OVH, rabbits demonstrated significantly depressed (Weaver 2010):
  - food consumption (days 1-7)
  - water consumption (days 1-4)
  - fecal output (days 1-2)
  - No significant differences were found between analgesic treatment groups (just pre and post-op)

SCORE	DESCRIPTION	PHOTO IDEAL
0	Fewer than 20-40 droppings. Poorly formed feces, usually tiny and distorted in shape (oval).	
1	1 handful droppings, all could be held in one hand. Mixture of normal (round) and poorly formed (oval).	
2	2 handfuls droppings, all could be held by both hands. Mostly normal (round), some distorted (oval).	
3	Multiple piles of droppings that could not be picked up by 2 hands. Almost all normal (round) form.	
4	Multiple piles of droppings that are dense and cover a large portion of the fecal collection tray.	

- Fecal output scoring system facilitated rapid quantification of fecal output by all staff members.
- Mean fecal output did not return to baseline until day 4 after OVH.
- No difference was found between treatment groups.
  - Including transdermal fentanyl and SQ buprenorphine treated groups.

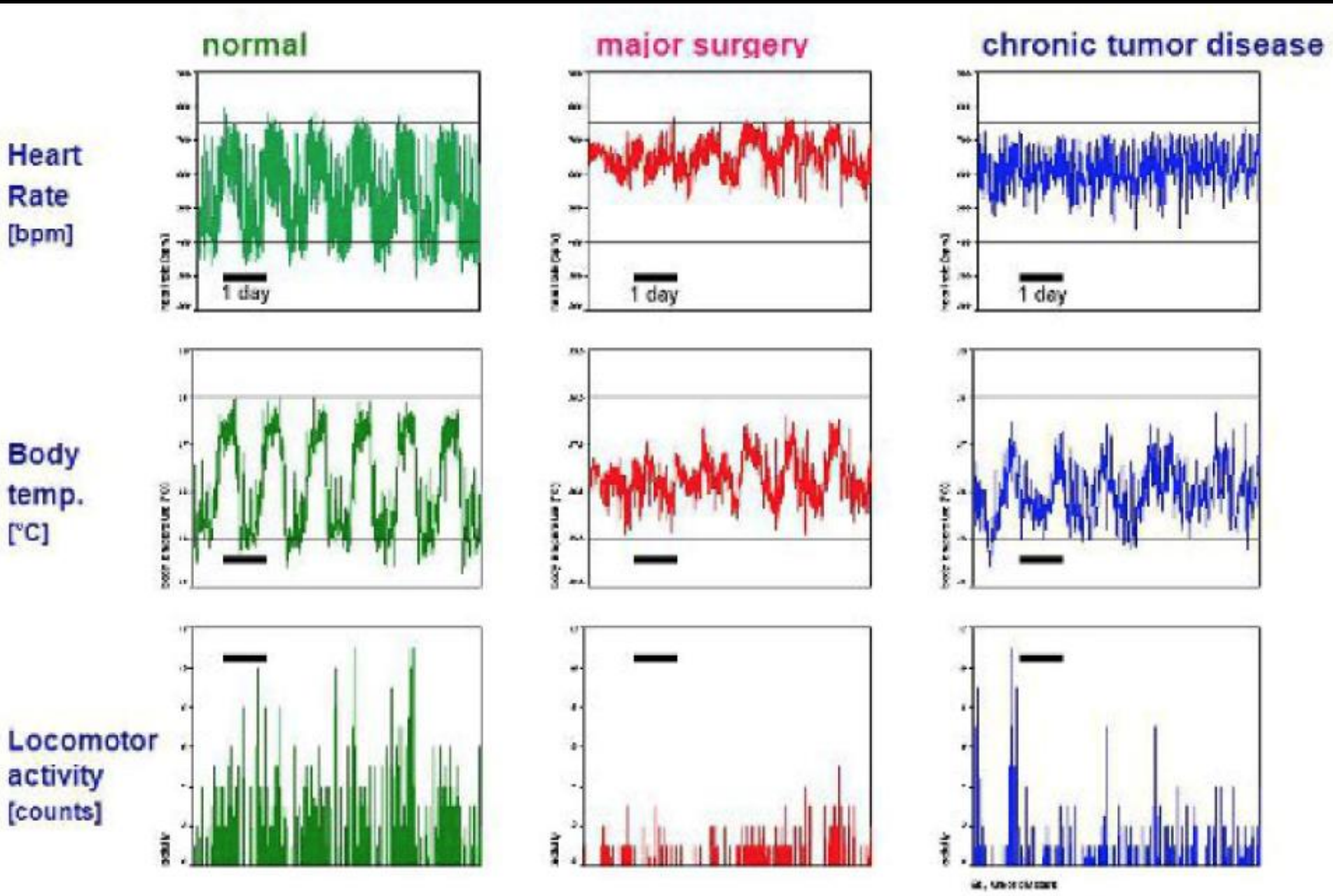
(Weaver 2010)

Fecal or Serum Corticosterone

- Not pain specific, often do not see effects of treatments:
  - Did not differ between analgesic groups treated after castration in mice. (Wright Williams 2013)
  - Was not correlated with postoperative pain and stress in vasectomized mice (Jacobsen, 2012)
  - Did not differ between sham and tattoo treatments in rabbits (Keating 2012)

Telemetry

- Benefits of remotely assessing free-moving animals
  - In mice, major surgery was followed by an increase in heart rate, particularly in the daylight phase, and depression of locomotor activity. (Cesarovic, 2011)
  - Tattoo in rabbits resulted in higher peak heart rate, as well as higher systolic and mean arterial blood pressure. EMLA prevented these changes. (Keating 2012)



Cesarovic, 2011

Pain Specific Behaviors

- wound licking
- hind-leg stretching
- twitch
- flinch
- pressing of the abdomen into the substrate while stretching
- abdominal writhing
  - Wright-Williams, 2013
  - Jacobsen, 2012
  - Leach, 2012

AHWLA
Assessing the Health and Welfare of Laboratory Animals

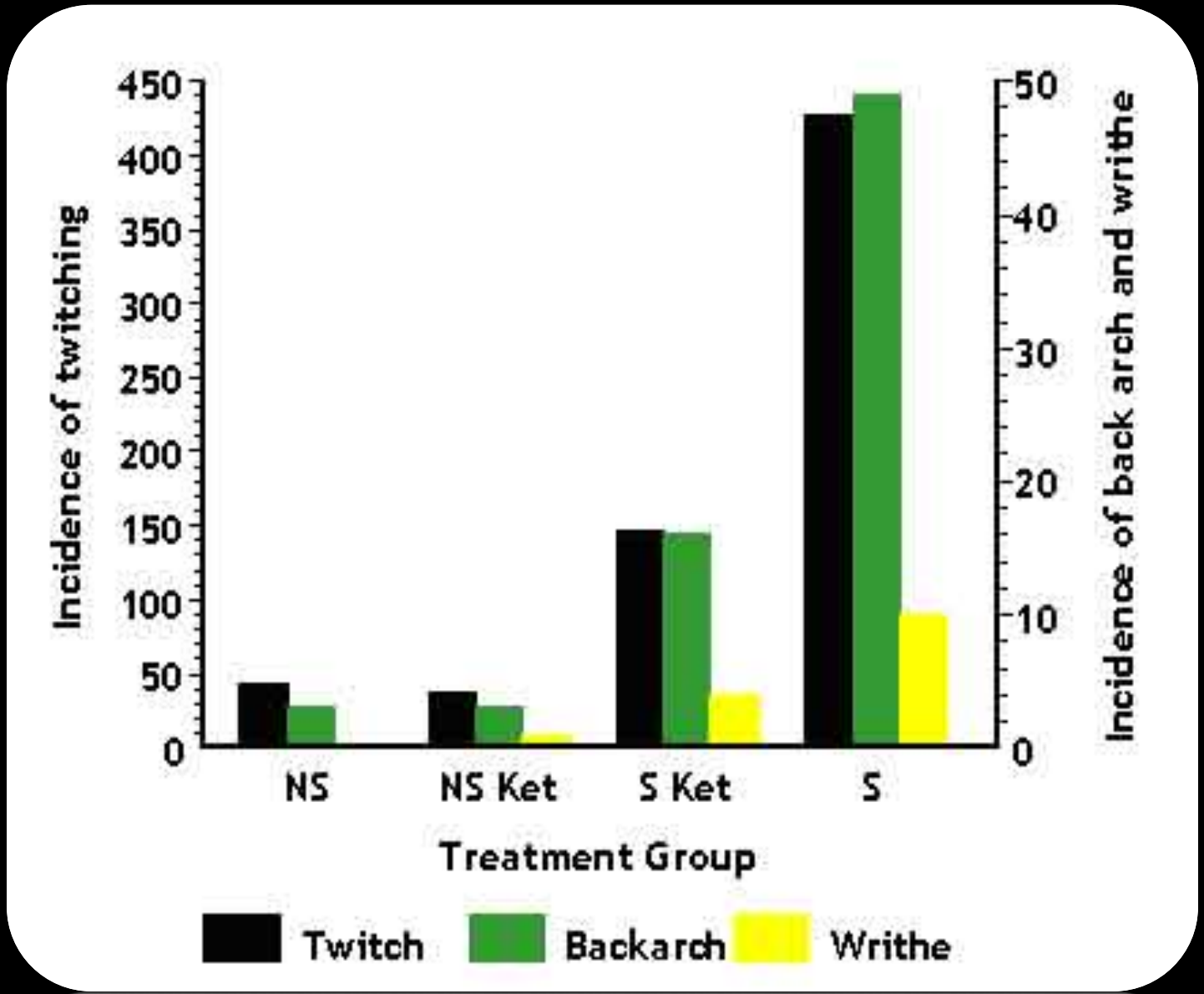
www.ahwla.org.uk

Changes in Body Posture in Mice

- In response to *abdominal* pain, mice demonstrate abdominal contractions, often accompanied by extension of the hind limbs.
- http://www.ahwla.org.uk/site/tutorials/RP/RP09-writhe480/RP09-writhe1.html
- http://www.ahwla.org.uk/site/tutorials/RP/RP09-sian480/RP09-sian1.html

Changes in rat body posture with abdominal pain

- Assessing the Health and Welfare of Laboratory Animals organization
- http://www.ahwla.org.uk/site/tutorials/RP/RP08-arch480/RP08-arch1.html



NS: No surgery S: Surgery Ket: Ketoprofen (NSAID)

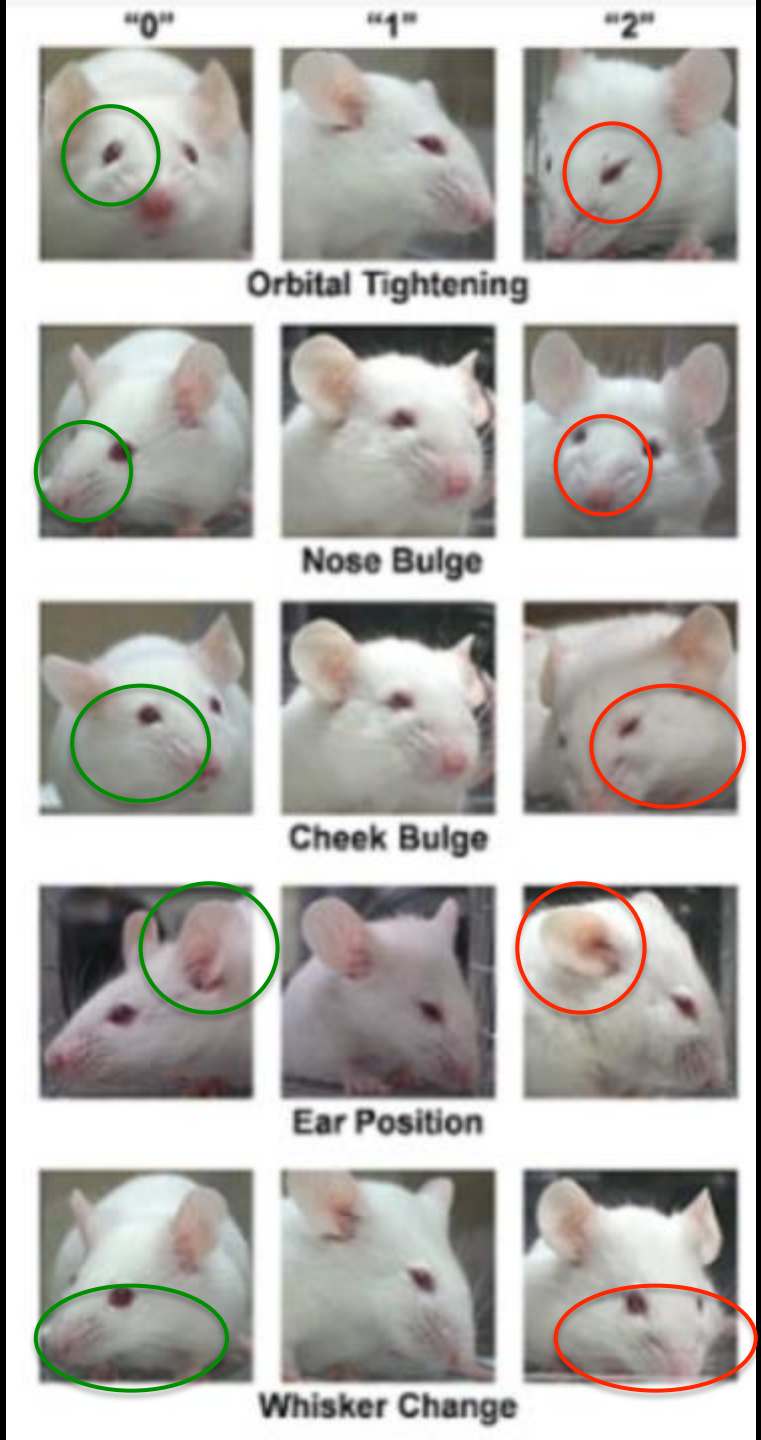
Roughan, J. V., Flecknell, P. A. 2001.

Pain Faces: Mice

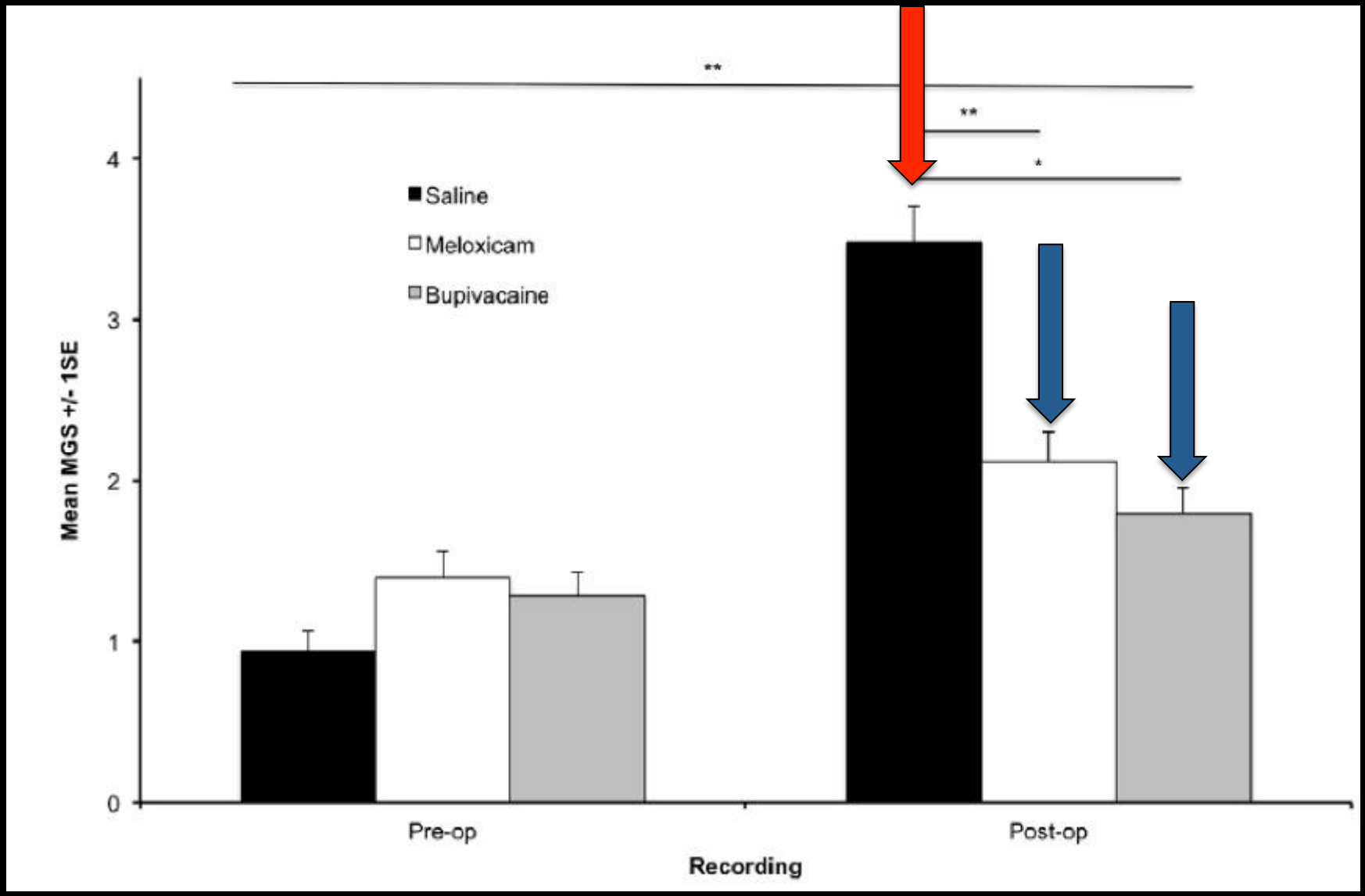
- Mouse Grimace Scale (MGS)
  - score a image of a mouse in which eyes and ears are visible.
  - Assign a value of 0, 1, or 2 for each of the 5 facial action units (FAUs): orbital tightening, nose bulge, cheek bulge, ear position, and whisker change.
  - Matsumiya, 2012
  - Leach, 2012

Pain Faces in Mice

- Langford, et al. 2010.
- 5 Facial Action Units
- Each unit scored on a basis of no pain (0), mild to moderate pain (1), severe pain (2).
- Correlated with traditional pain measures used in the laboratory.



MGS Detects Post-Operative Pain



- Leach et al, 2012

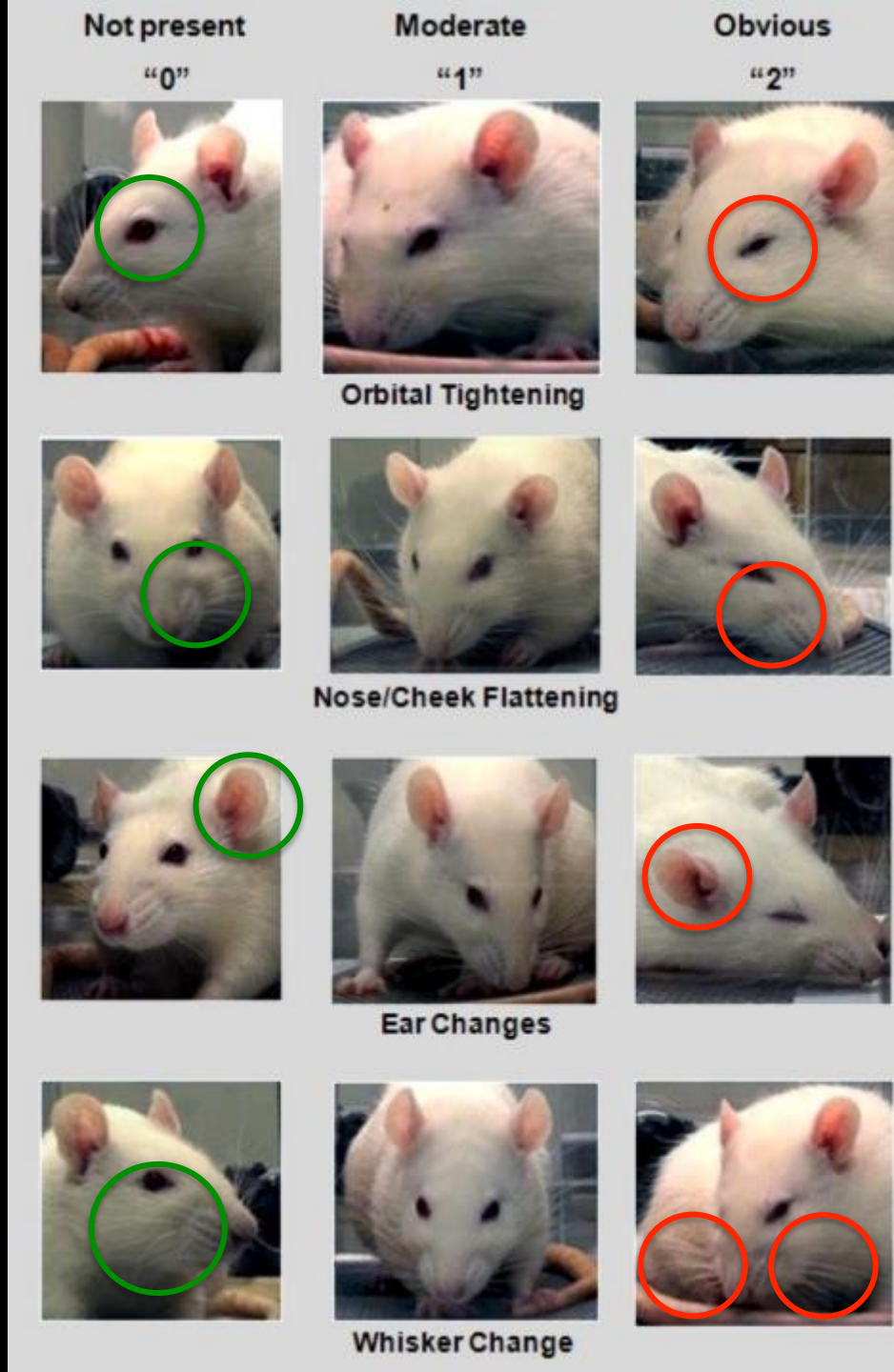
1 hr post vasectomy

Pain Faces: Rats

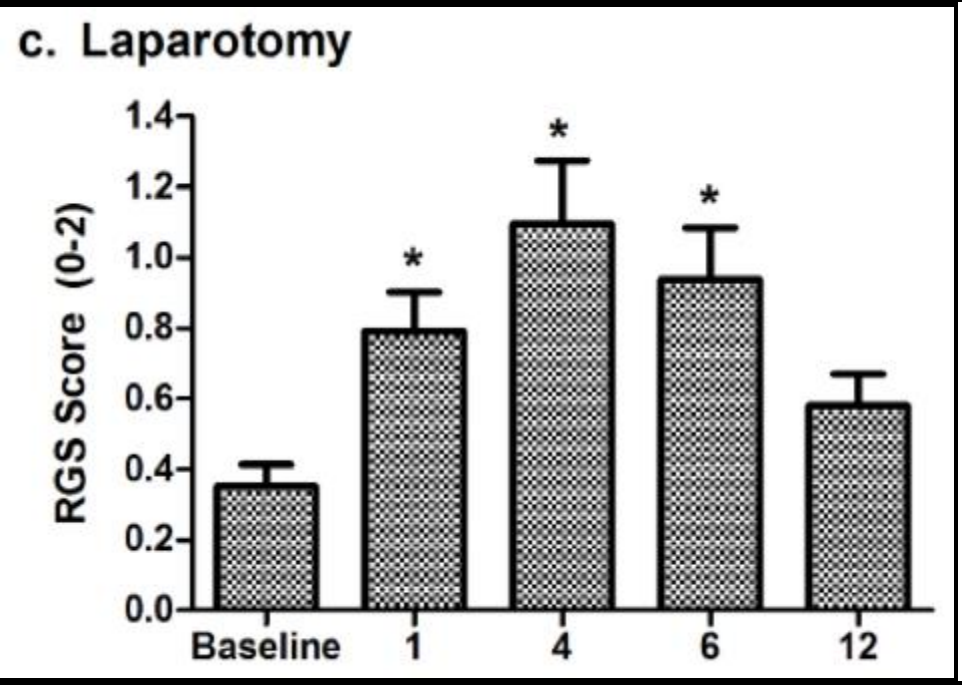
- Rat Grimace Scale (RGS) (Sotocinal, 2011)
  - score image of face and shoulders
  - Scale is 0-2 on four facial action units (FAUs):
    - Orbital Tightening
    - Nose/Cheek Flattening
    - Ear Changes
    - Whisker Change.

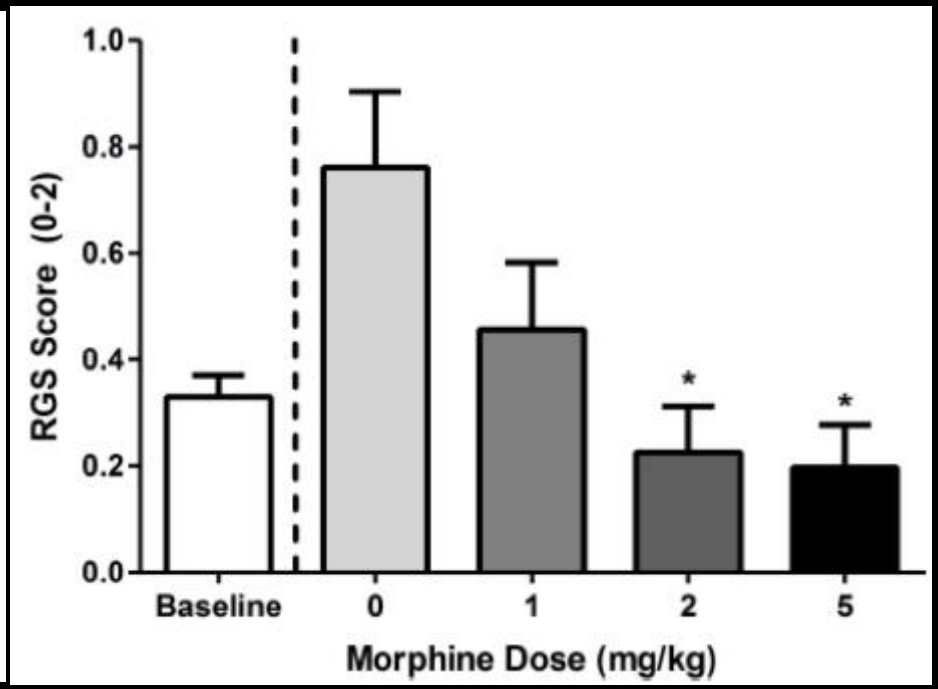
Rat Pain Face

- Sotocinal, et al. 2011.
- **Orbital Tightening**: Rats in pain display a narrowing of the orbital area, manifesting either as (partial or complete) eye closure or eye "squeezing."
- **Nose/Cheek Flattening**: Rats in pain display successively less bulging of the nose and cheek, with eventual absence of the crease between the cheek and whisker pads.
- **Ear Changes**: The ears of rats in pain tend to fold, curl and angle forwards or outwards, resulting in a pointed shape. The space between the ears may appear wider.
- **Whisker Change**: The whiskers of rats in pain move forward (away from the face) from the baseline position, and tend to bunch, giving the appearance of whiskers standing on end.



Using the rat grimace score





Pain Faces: Rabbits

- Rabbit Grimace Scale (RbtGS) (Keating, 2012)
  - Score image of face and shoulders
  - Scale of 0-2
  - Five facial action units (FAUs);
    - orbital tightening
    - cheek flattening
    - nose shape
    - whisker position
    - ear position

Rabbit Pain Face

- Keating et al, 2012.

Orbital Tightening

Not Present (0) | Moderately Present (1) | Obviously Present (2)

The eyelid is partially or completely closed. The globes themselves may also be drawn in toward the head so that they protrude less. If the eye closure reduces the visibility of the eye by more than half, it would be scored as '2' or 'obviously present'.

Cheek Flattening

Not Present (0) | Moderately Present (1) | Obviously Present (2)

Contraction around the muzzle so that the whisker pads are pressed against the side of the face. The side contour of the face and nose is angular and the rounded appearance of the cheeks to either side of the nose is lost.

Nose Shape

Not Present (0) | Moderately Present (1) | Obviously Present (2)

The nares (nostril slits) are drawn vertically creating a more pointed nose that resembles a 'V' more than a 'U'. The tip of the nose may also be tucked under towards the chin exaggerating this appearance.

Whisker Position

Not Present (0) | Moderately Present (1) | Obviously Present (2)

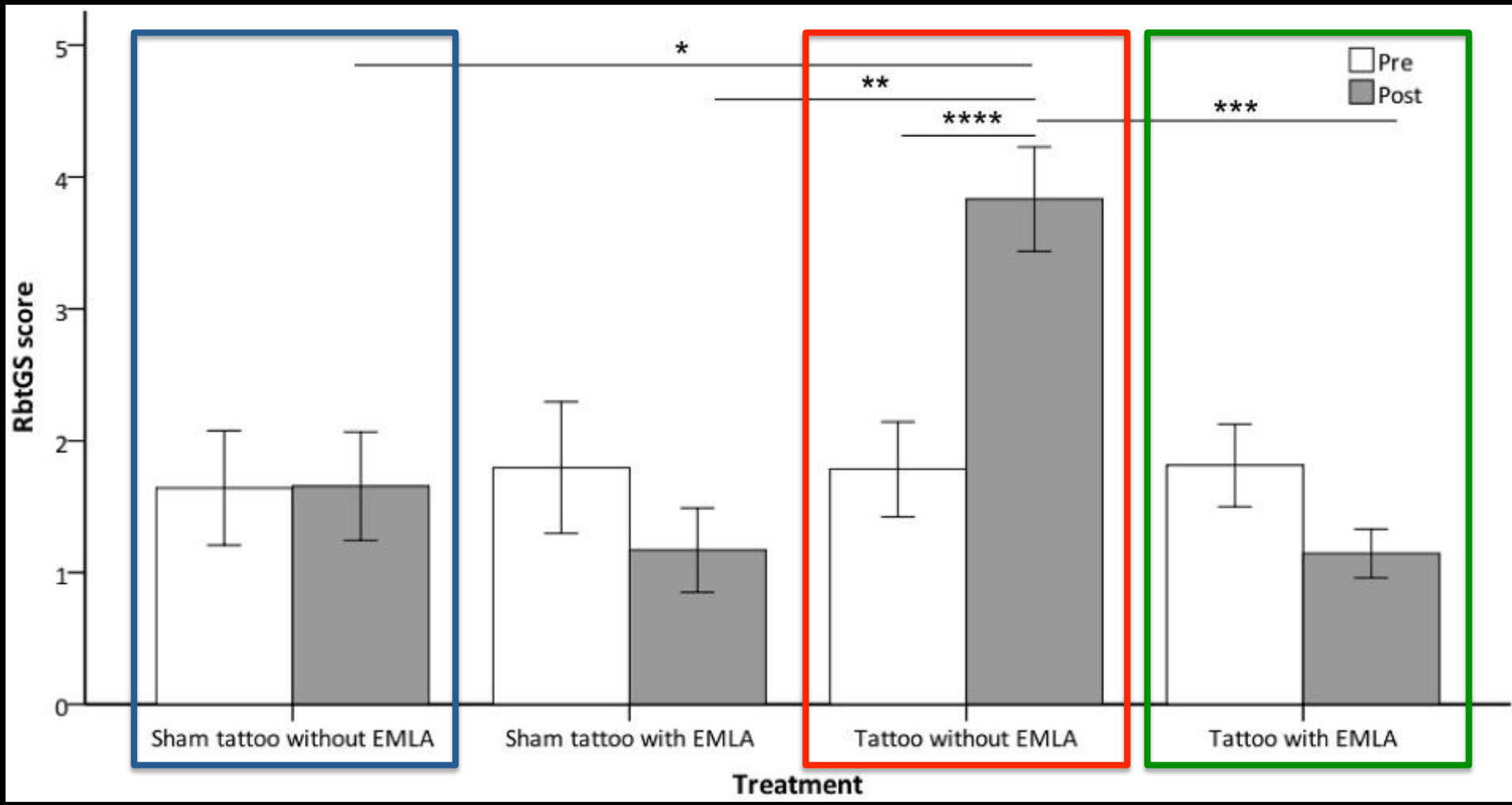
Whiskers are straightened and extended horizontally or pulled back toward the cheeks instead of the normal position where whiskers tend to have a gentle downward curve.

Ear Position

Not Present (0) | Moderately Present (1) | Obviously Present (2)

Normally the ears are roughly perpendicular to the head, facing forward or to the side, held in an upright position away from the back and sides of the body with a more open and loosely curled shape. In pain the ears rotate away from normal position to face towards the hindquarters, tend to move backward and be held closer to the back or sides of the body and have a more tightly folded or curled shape (i.e. more like a tube).

Rabbit grimace scale to detect pain



EMLA cream is a lidocaine cream that provides local anesthesia - in this case to the ear prior to ear tattoo application (clamp).

Challenges to observing pain:

- Rodents and rabbits are prey species
- Do NOT exhibit the familiar 'fight or flight' response, instead they exhibit 'Conservation withdrawal' response.
  - to many observers a very painful rodent appears to be "QAR, sleeping/resting comfortably"

What we see…

What they see…

Loss of Normal Behaviors

- Activity
  - Automated behavioral analysis of mouse behavior, specifically walk and jump, was was significantly depressed after surgery (Leach 2012)
    - Unable to distinguish between analgesia vs. saline groups.
- Distance traveled
  - Mean travel distance and rearing in rabbits after OVH (Weaver 2010).
- Wheel running
  - CFA-induced decrease in voluntary wheel running in mice was dose-dependently reversed by subcutaneous administration of NSAIDs and opioids (Cobos 2012)

Table 1. The HomeCageScan scored behaviours that significantly decreased in frequency from pre to post vasectomy.

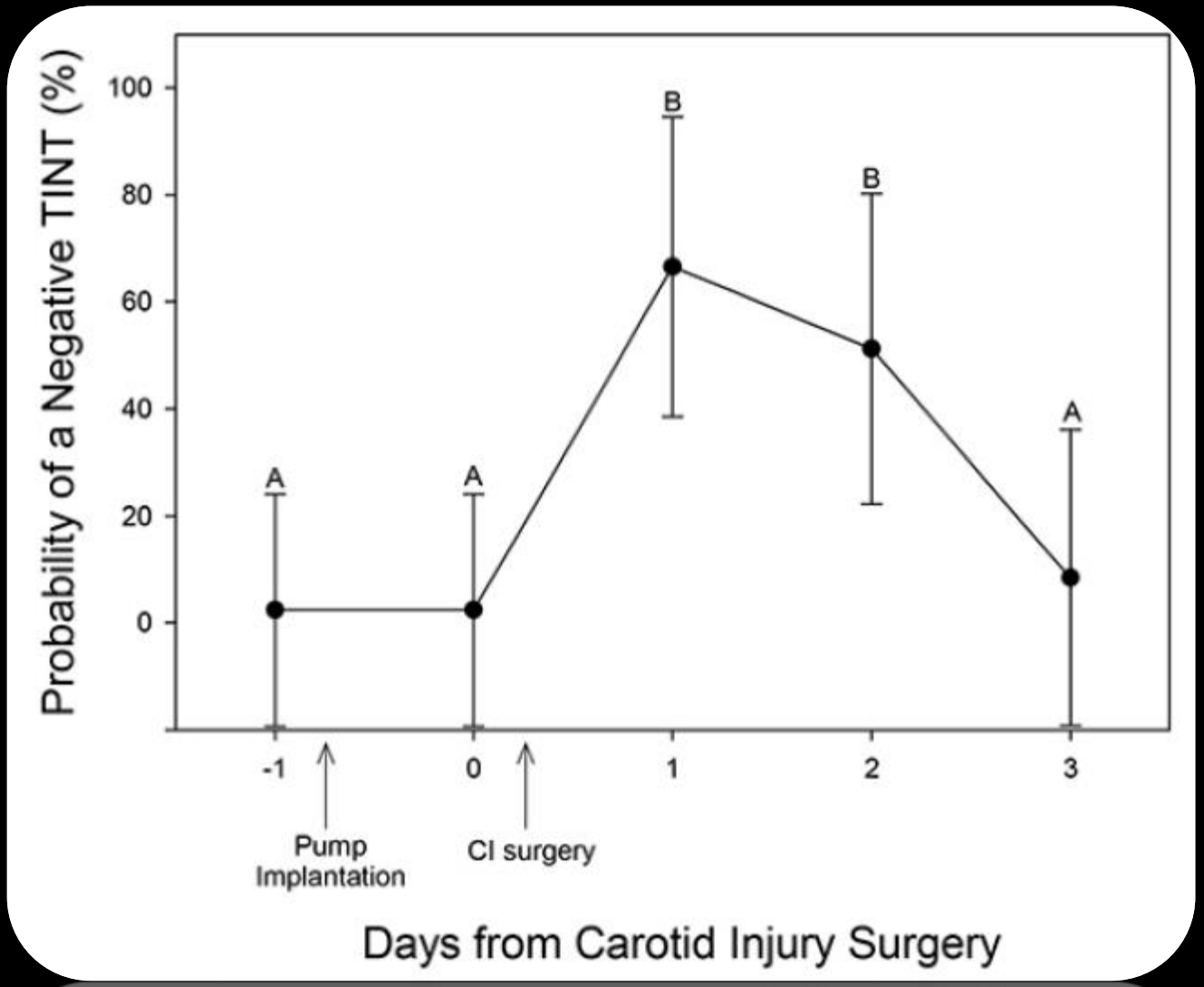
Behaviour (P-value)	
Come down (P = 0.000)	Jump (P = 0.000)
Rear up (P = 0.000)	Come down to partial rear (P = 0.001)
Remain rear up (P = 0.000)	Rear up from partial rear (P = 0.003)
Stretch (P = 0.002)	Unknown (P = 0.008)
Land vertically (P = 0.000)	Remain hang vertically (P = 0.01)
Walk left (P = 0.000)	Hang vertically from rear up (P = 0.000)
Walk right (P = 0.000)	Turn (P = 0.048)
Walk slow (P = 0.002)	Rear up to partial rear (P = 0.052)

Leach, 2012

Nesting

- Time-to-integrate-to-nest test (TINT score) (Rock, 2014)
  - mice are acclimated to nesting for several days
  - small amount of nesting material added to cage
  - if it is integrated into the main nest site within 10 min a positive TINT is assigned
  - failure to interact with the nesting material within 10 min was a negative TINT score.

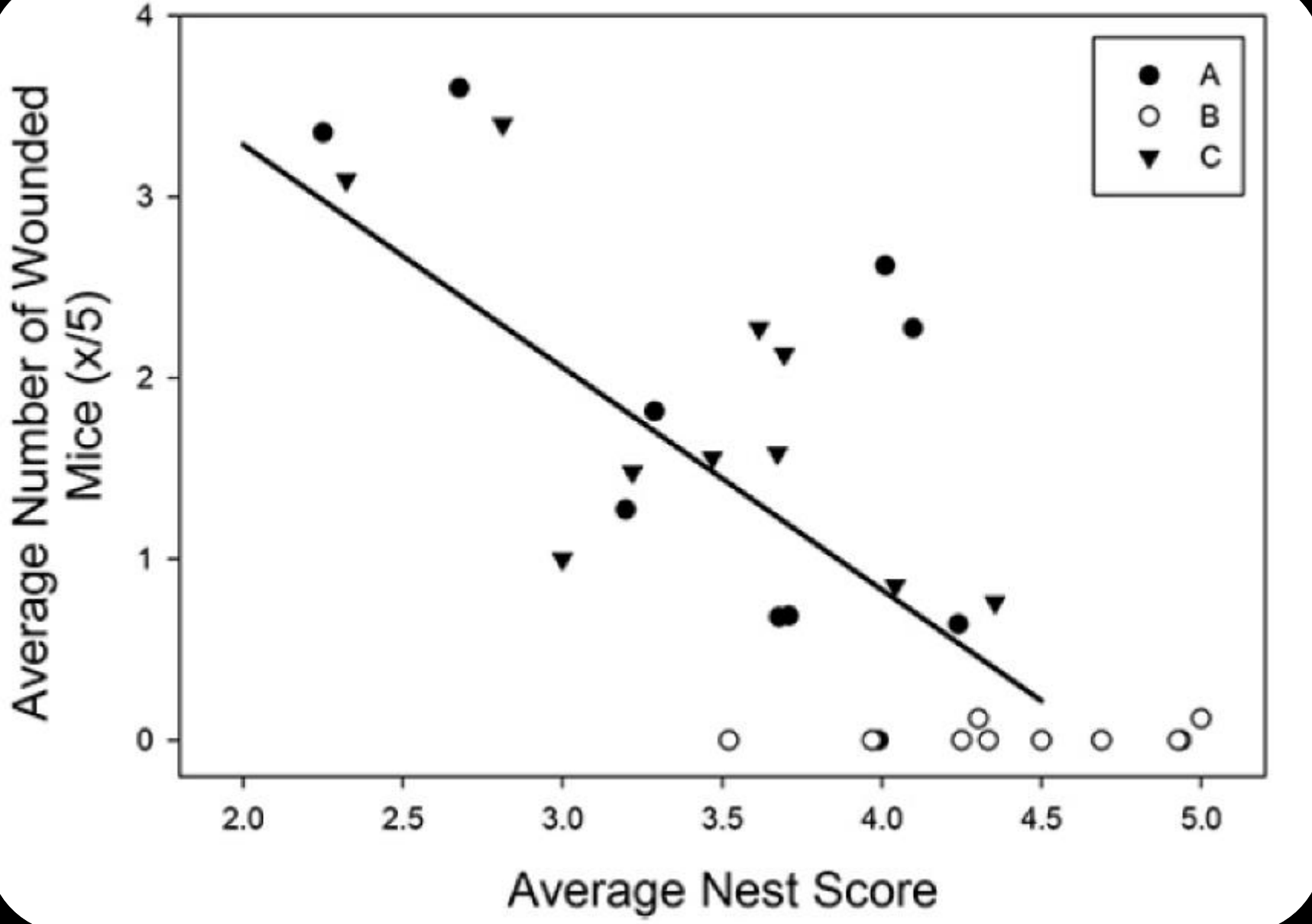
TINT Score



Rock, 2014

Nesting

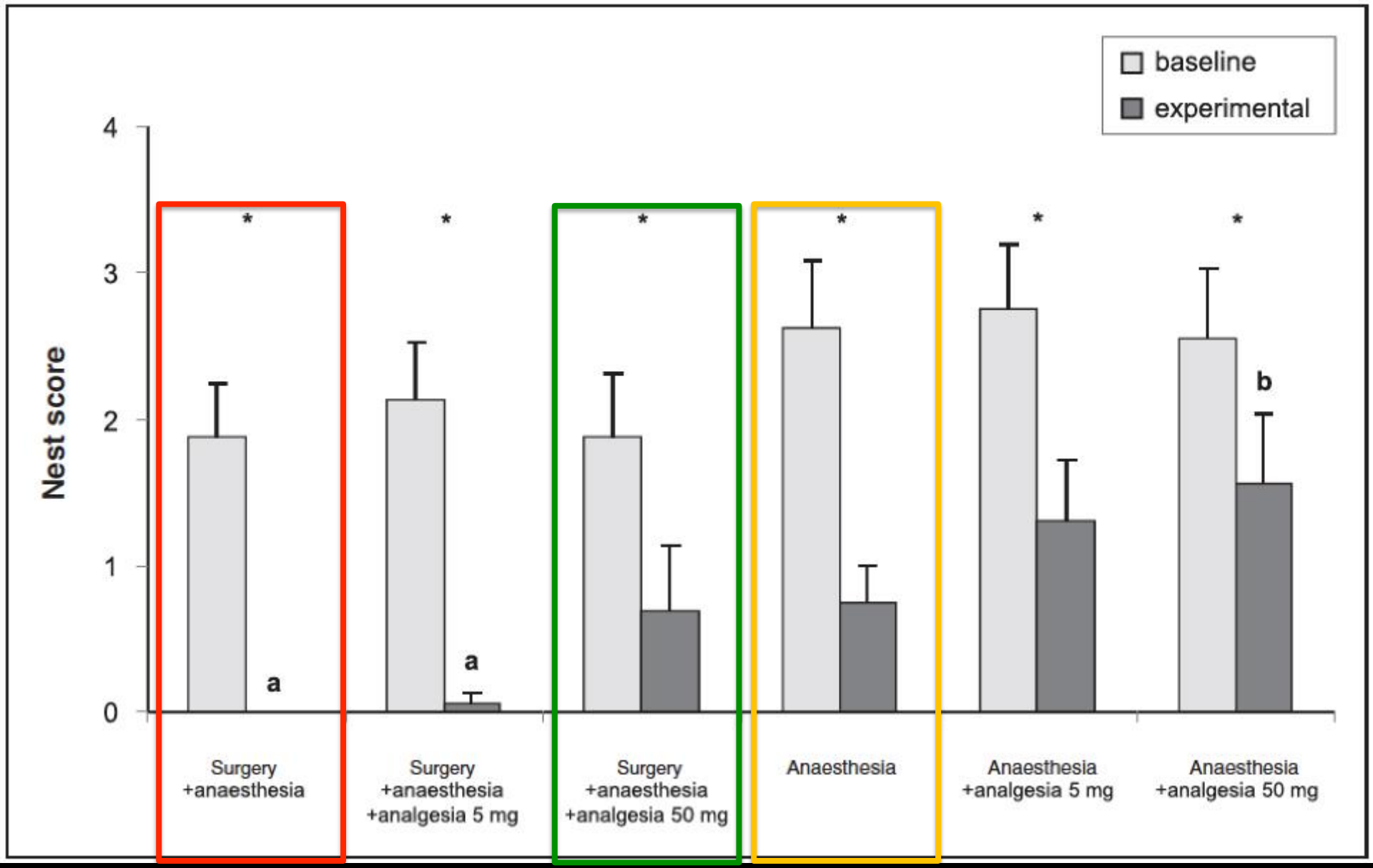
- Nest complexity (Gaskill, 2013)
  - place nesting material in cage and return 7-9 hours after lights-on to score.
  - Score ranges from 0 (material untouched) to 5 (nest walls are taller than ½ the height of a dome).

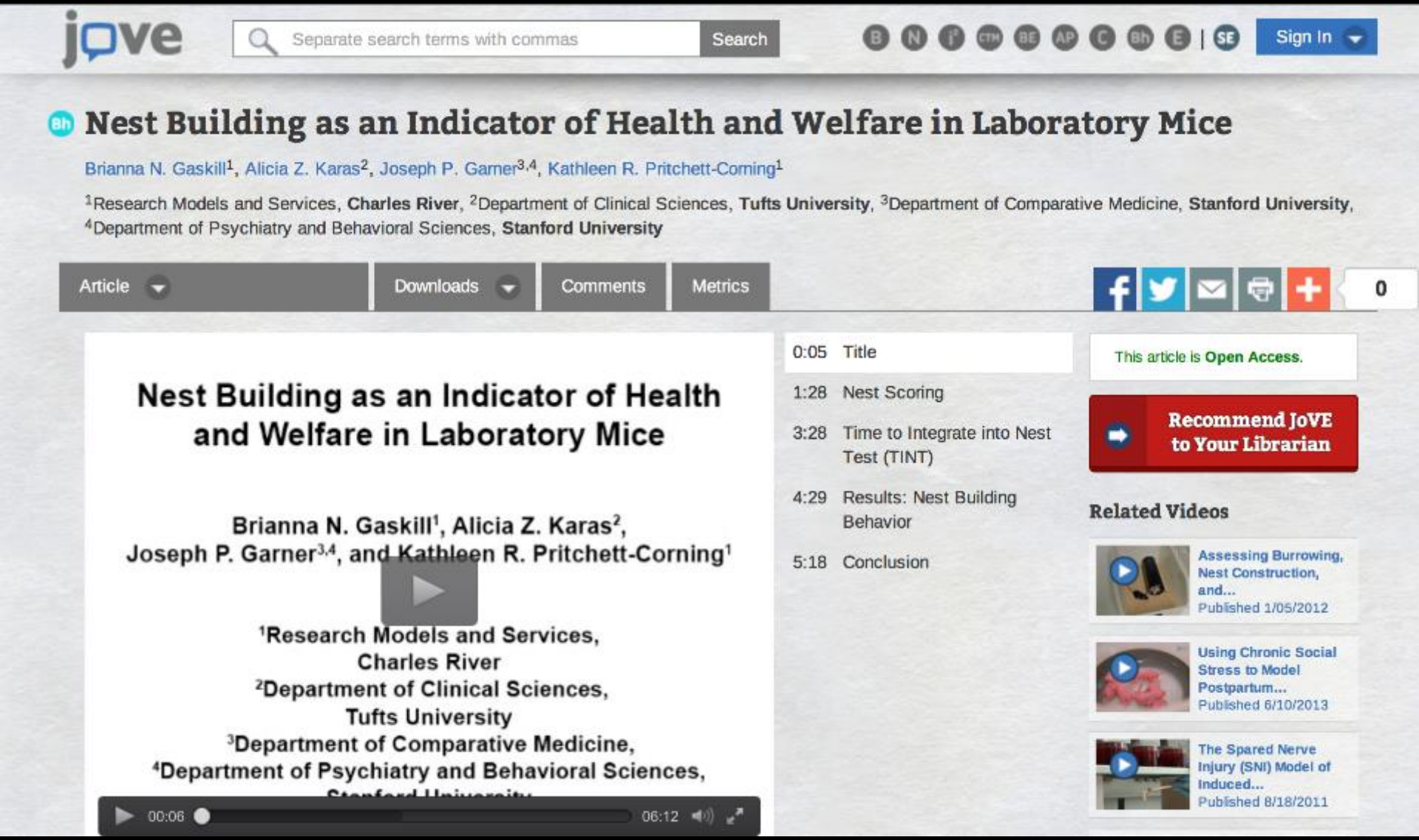


Gaskill, 2013

Nesting

- Latency to nest building (Jirkof, 2013)
  - Time from provision of nestlet to manipulating or carrying the nestlet or nestlet material for more than 3 s.


baseline
experimental
Nest score
4
3
2
1
0
*
*
*
*
*
*
a
a
b
Surgery +anaesthesia
Surgery +anaesthesia +analgesia 5 mg
Surgery +anaesthesia +analgesia 50 mg
Anaesthesia
Anaesthesia +analgesia 5 mg
Anaesthesia +analgesia 50 mg



http://www.jove.com/video/51012/nest-building-as-an-indicator-of-health-and-welfare-in-laboratory-mice

Gaskill, 2013

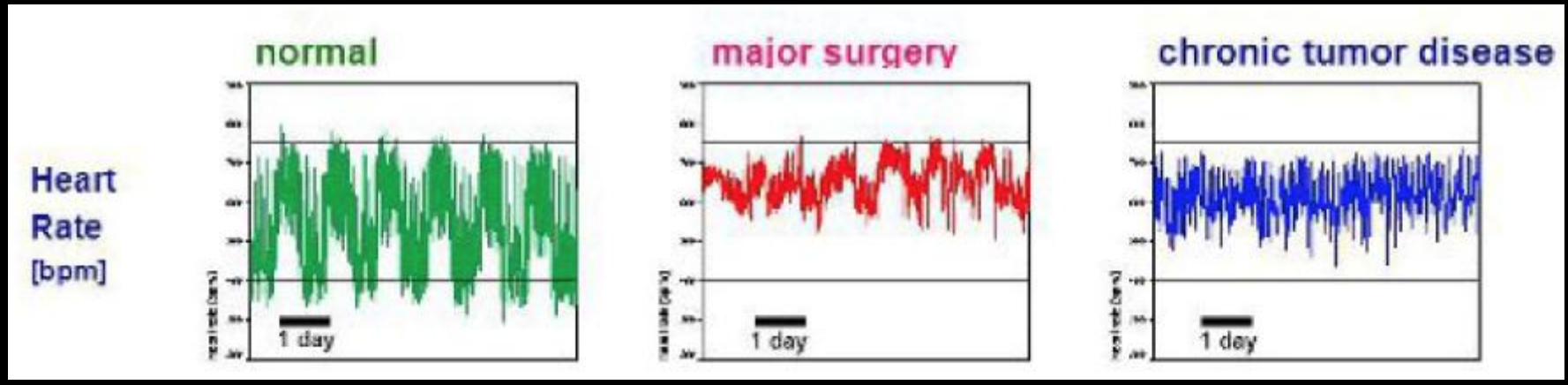
Pain Assessment *Recommendations*

- Consumption/Body Weight/Fecal Production
  - Easy to measure
  - Reliable indicator of distress
  - Retrospective – can take 24 hours to observe.
  - Good practice as part of standard husbandry care.

- Corticosterone
  - Did not correlate to pain. Not recommended.

Pain Assessment *Recommendations*

- Telemetry
  - May not be pain specific.
  - Require surgery for implantation – not practical for high throughput or cage-side use.

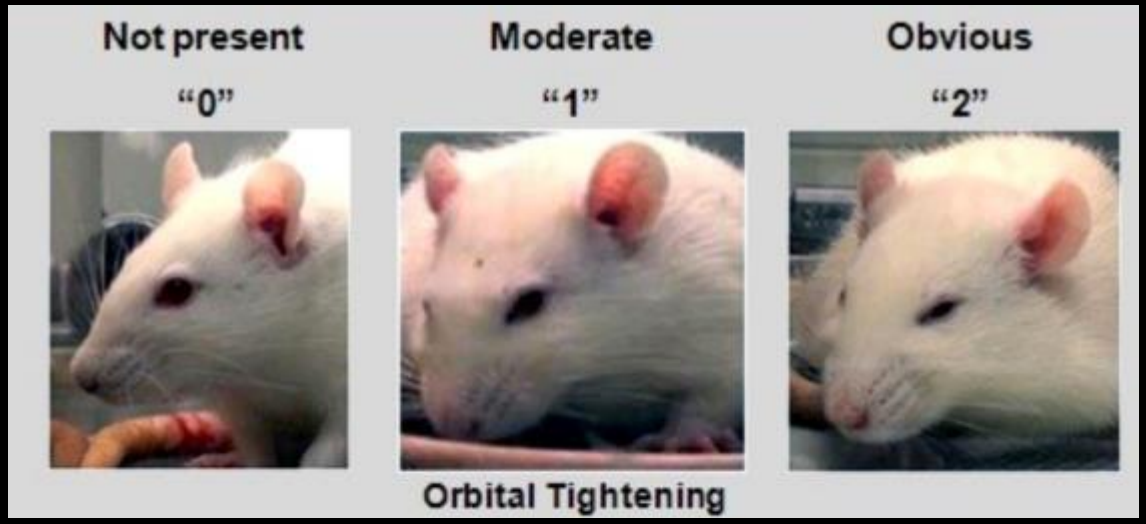


Pain Assessment *Recommendations*

- Nesting:
  - Measuring latency to nesting or evaluating nest quality may not be pain specific.
  - However, it is an easy, first line cage-side assessment for identifying animals in need of veterinary attention.
  - If normals are established, can assess a large number of cages in matter of minutes

Pain Assessment *Recommendations*

- Pain Faces and Pain Specific Behavior
  - Once identify animals in need of veterinary attention, use to evaluate presence and severity of unalleviated pain.
  - May take more time, but is pain specific.

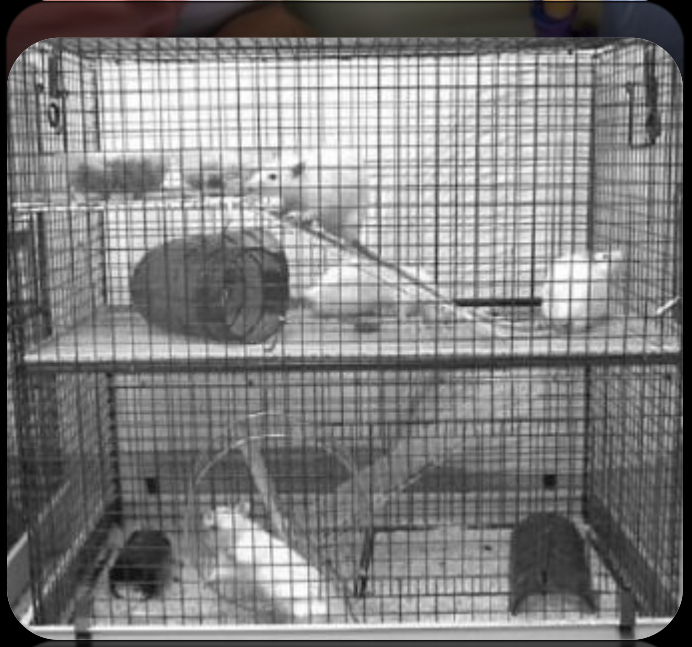


Hot Topics in Analgesia

- Pain Assessment
- Non-pharmacologic Analgesia
- Oral Dosing of Analgesia
- Sustained Release Analgesia
- Tramadol
- Multimodal Analgesia
- Transdermal Analgesia
- Regional Analgesia

Non-pharmacologic Analgesia Approaches

- Acupuncture
- Cryoanalgesia
- Social Housing
- Enrichment



Acupuncture

- Acupuncture treatments resulted in significant improvement in mobility in chimps with osteoarthritis pain. (Magden, 2014)

1	Never displays impeded locomotion or impaired mobility
2	Infrequent slightly or mildly impaired locomotion
3	Frequent slightly or mildly impaired locomotion
4	Infrequent moderately impaired locomotion
5	Frequent moderately impaired locomotion
6	Infrequent severely impaired locomotion
7	Frequent severely impaired locomotion
8	Continuously impaired locomotion

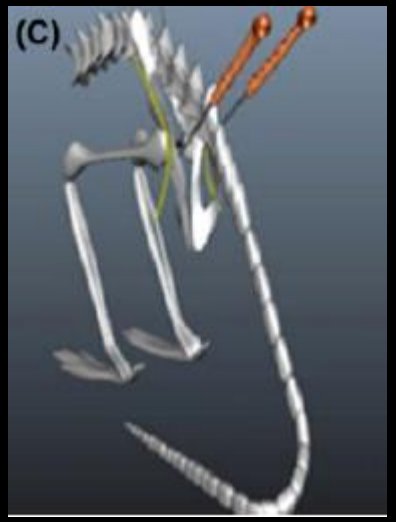
Better

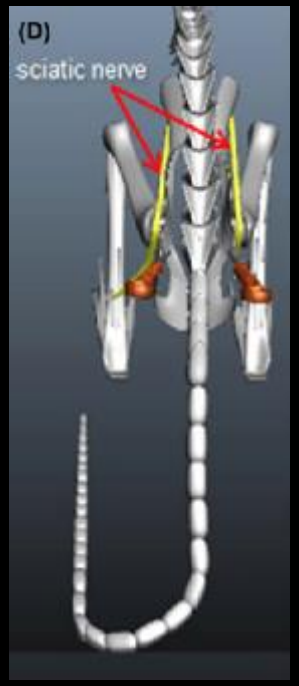
Worse

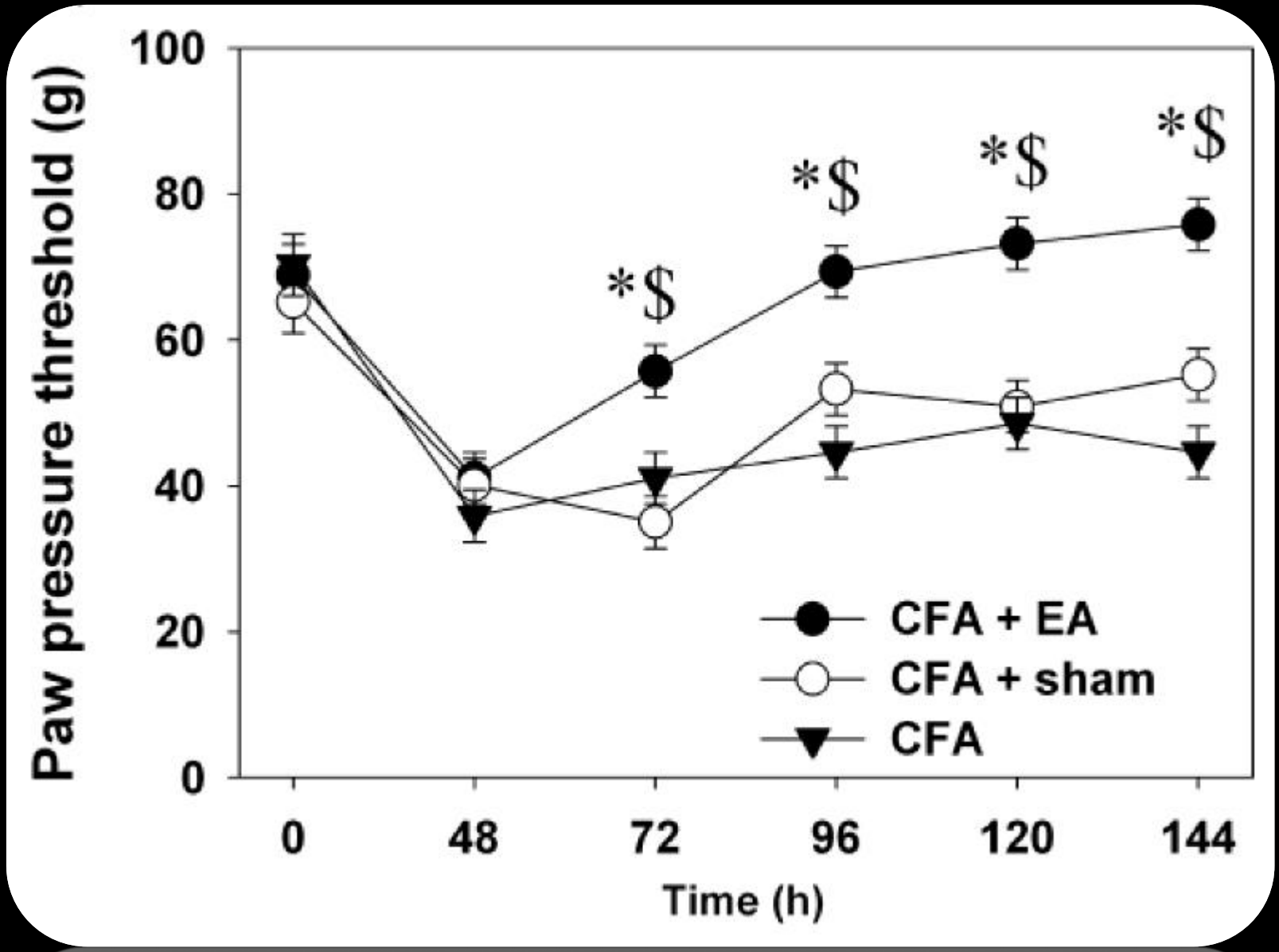
Figure 4. Scoring system for assessing mobility and locomotion.

Acupuncture

- Electroacupuncture (EA) in rats:
  - Inhibited neuropathic pain after spinal ligation surgery. (Jiang, 2013)
  - Reduced thermal and mechanical nociception, as well as paw inflammation after intraplantar CFA injection. (Wang, 2013)






Paw pressure threshold (g)
100
80
60
40
20
0
0
48
72
96
120
144
Time (h)
*$
*$
*$
*$
CFA + EA
CFA + sham
CFA

(Wang, 2013)

Cryoanalgesia

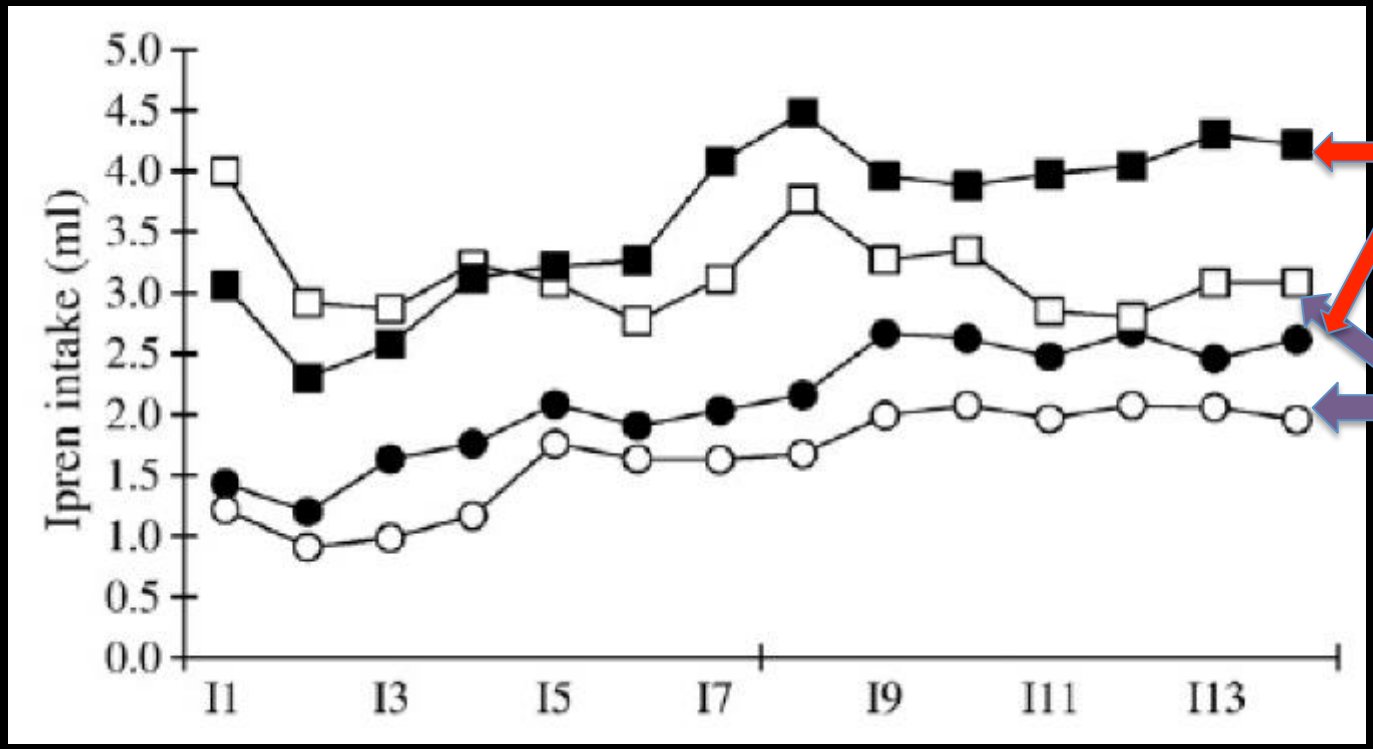
- Topical vapocoolant for local anesthesia for tail biopsies in preweanling mice:
  - Significant increase in tail pinch latency and had significantly lower increase in blood glucose. However, more licking and re-bleeding (Matthias, 2013).
  - Struggled more, had more bleeding, erythema, and swelling, which persisted for up to 12 h (Paluch 2014).
- Did not significantly improve behavioral response to tail biopsy in adult mice (Jones, 2012).

What did work for tail biopsies:

- In pre-weanling mice, immersion of tail after biopsy in bupivacaine for 30s decreased tail grooming for 30 min.
- Buprenorphine if provided 20-30 min before biopsy.
- Jones, 2012

Social Housing & Self-Administration

- Post-operatively, individual housing and barren caging resulted in greater post-operative self administration of ibuprofen water (Pham, 2010).



Individually housed

Barren

Group housed

Enriched

Social Housing

- Anesthesia and surgery resulted in clear changes in behavior, but differences between individual and pair housing conditions were minor.
  - Pair housed mice had a shorter latency to burrowing, possibly reflecting faster recovery
  - (Jirkof, 2012)

Social Housing & Enrichment

- In a model of chronic pain, rats housed socially with enrichment reduced allodynia from 4 to 3 weeks. (Gabriel 2010)

- Socially housed mice recovered quicker and showed less stress following telemetry implantation compared to both singly housed grid separated mice. (Van Loo, 2007)

Recommendations for Non-Pharmacologic Analgesia Approaches

- Acupuncture appears to be a promising therapy for both post-operative and chronic pain.
- Cryoanalgesia was not ideal for preventing pain associated with tail biopsies.
  - Dipping tail in bupivicaine or providing buprenorphine was effective.
- Social housing and enrichment sped recovery and reduced analgesic self administration.

Analgesics provided orally

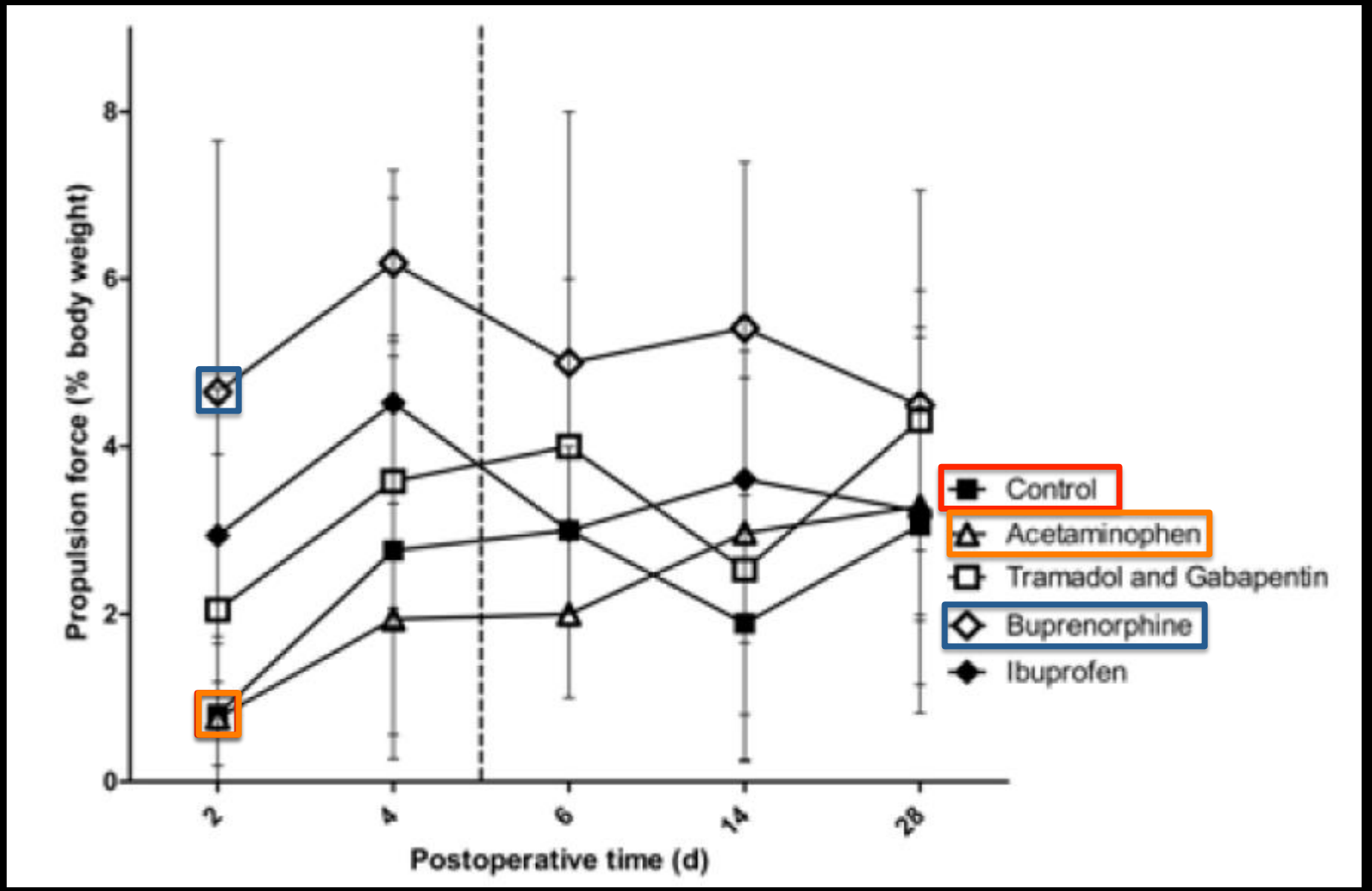
- Acetaminophen
- NSAIDS
- Buprenorphine

Oral Acetaminophen

PRO
Increased voluntary home cage wheel running after CFA/IFA injection.
Longer latency to withdrawal on hot plate test than non-medicated water control.
Increased consumption of medicated water after surgery.
If provide both medicated gel and water, can reach targeted dose of 200 mg/kg.

Christy, 2014; Caro, 2014; Matsumiya, 2012; Kolstand, 2012; Mickley, 2006; Bauer, 2003; Speth, 2001; Cooper 1997

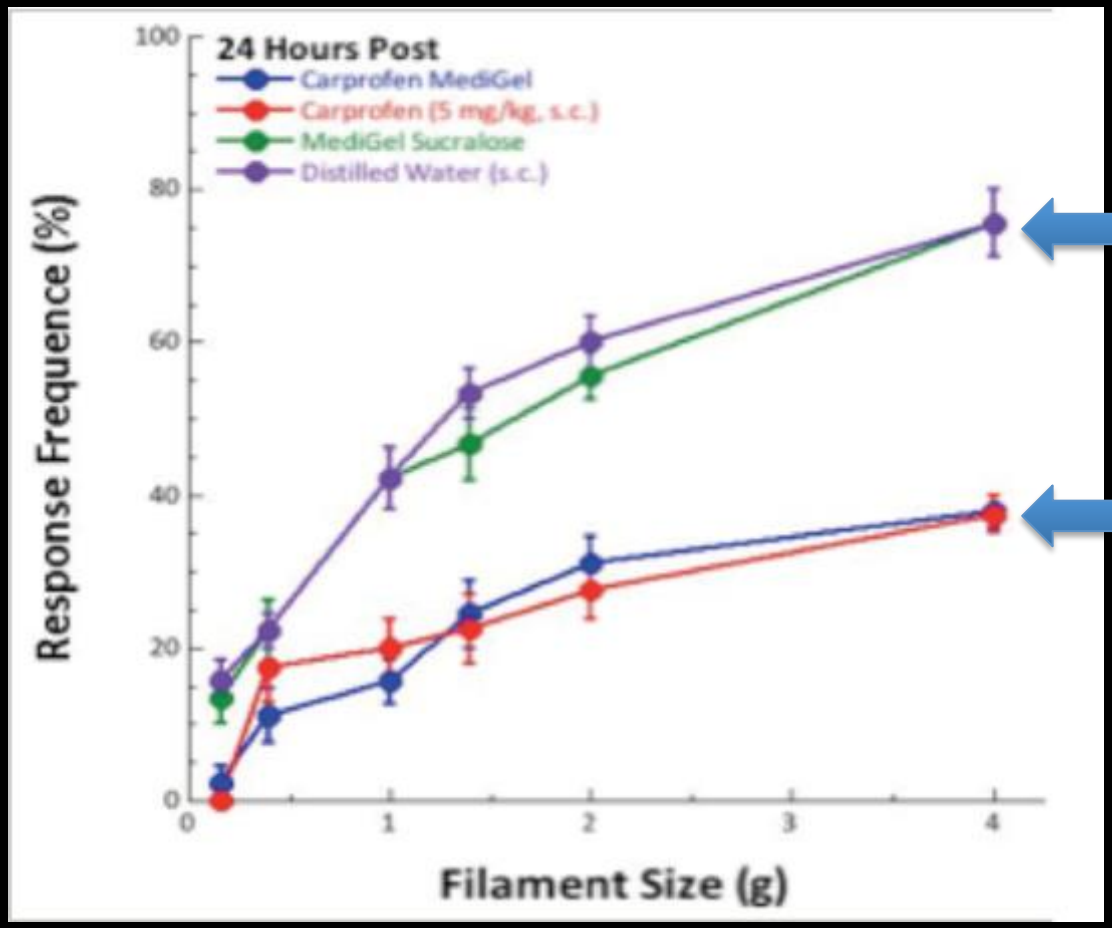
Acetaminophen failed to alleviate post-operative pain



Oral NSAIDS

PRO
Mice drinking water with liqui-gel ibuprofen consumed more food/water, showed less pruritic behavior, had greater healing of ulc derm lesions and greater locomotor activity.
After surgery, individually housed and non-enriched mice increased ibuprofen water self-administration.
Meloxicam and carprofen were stable in aqueous solutions when held for 7 d in dark, light, and cold environmental conditions.
Mice readily consumed carprofen-medicated water.
No gross or microscopic evidence of toxicity was seen in mice provided carprofen or meloxicam in drinking water.

Carprofen Medigel: post OVH in mice



Provision of distilled water or sucralose Medigel

SC injection of 5mg/kg Carprofen or provision of Carprofen Medigel

Presented at AALAS. N = 3 per group. Needs to be assessed in peer-reviewed publication

https://clearh2o.com/images/Nutritionals/MediGel%20CPF%20Sheet%20for%20AALAS%20Show-7.pdf

Caveats to NSAIDs

- Combining Paracetamol with either ibuprofen, meloxicam, or celecoxib (via gavage) augmented analgesia and exacerbated gastrotoxicity and nephrotoxicity. (Kumar 2010)

- A single 5-mg/kg dose of ketoprofen caused acute mucosal damage to the rat small intestine (Shientag 2012).

Oral Buprenorphine

PRO
Buprenorphine extruded diet pellets increased thermal latency on hot-plate test (equianalgesic to SC).
Better food & water intake, less post-op weight loss, and reduced corticosterone levels.
Voluntary ingestion or gavage resulted in a plasma concentrations above 1 ng/ml for 14 hrs compared to only 2 hrs when administered IV or SC.
A single injection of buprenorphine followed by buprenorphine in the drinking water induced an earlier onset of analgesia than buprenorphine in drinking water alone.

Oral Dose Analgesia *Recommendations*

- Acetaminophen:
  - Limited evidence for analgesic efficacy
  - Must overcome significant neophobia
- Carprofen and Ibprofen:
  - Some evidence for analgesic efficacy
  - Alleviated discomfort associated with ulcerative dermatitis.
- Buprenorphine:
  - Provided in water, food pellet or Nutella promising.
    - Some analgesic efficacy and appropriate seurm concentrations.
  - Can still have side effects of opiates – sedation, decreased food intake, hyperthermia.

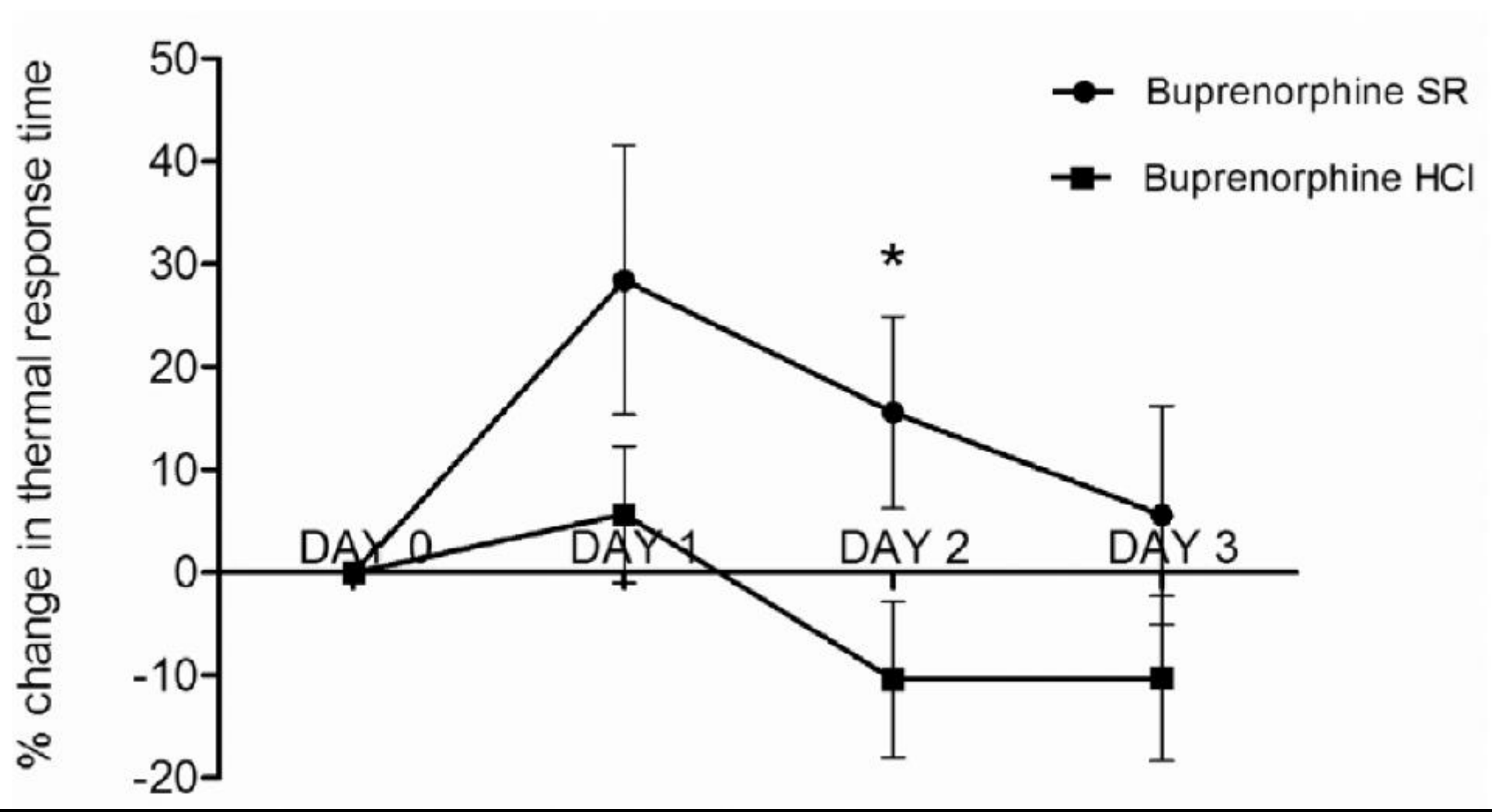
Sustained Release Analgesia

- BupSR (ZooPharm)

Buprenorphine SR

- Mice: (Carbone, 2011)
  - increased thermal latency up to 12 hours
  - Majority of mice developed scabs at site of injection
- Rats: (Chum, 2014 ; Foley, 2011)
  - Marked sedation at high doses but evidence of analgesia at lower doses for up to 48-72 hours.
  - Some skin irritation and scabbing noted
  - Plasma concentrations remained over 1 ng/mL for 72 h after a single dose
    - In humans, the minimal effective analgesic concentration is 0.1 ng/mL, target plasma concentration is 0.5 to 0.7 ng/mL

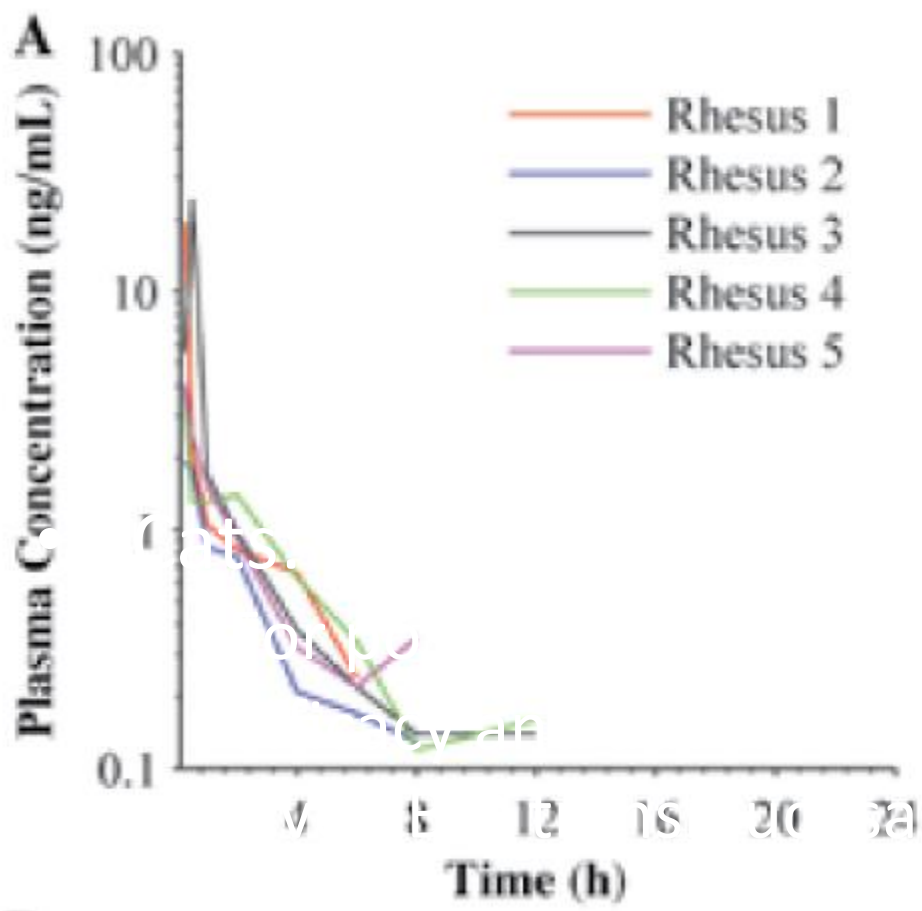
BupSR in Rats

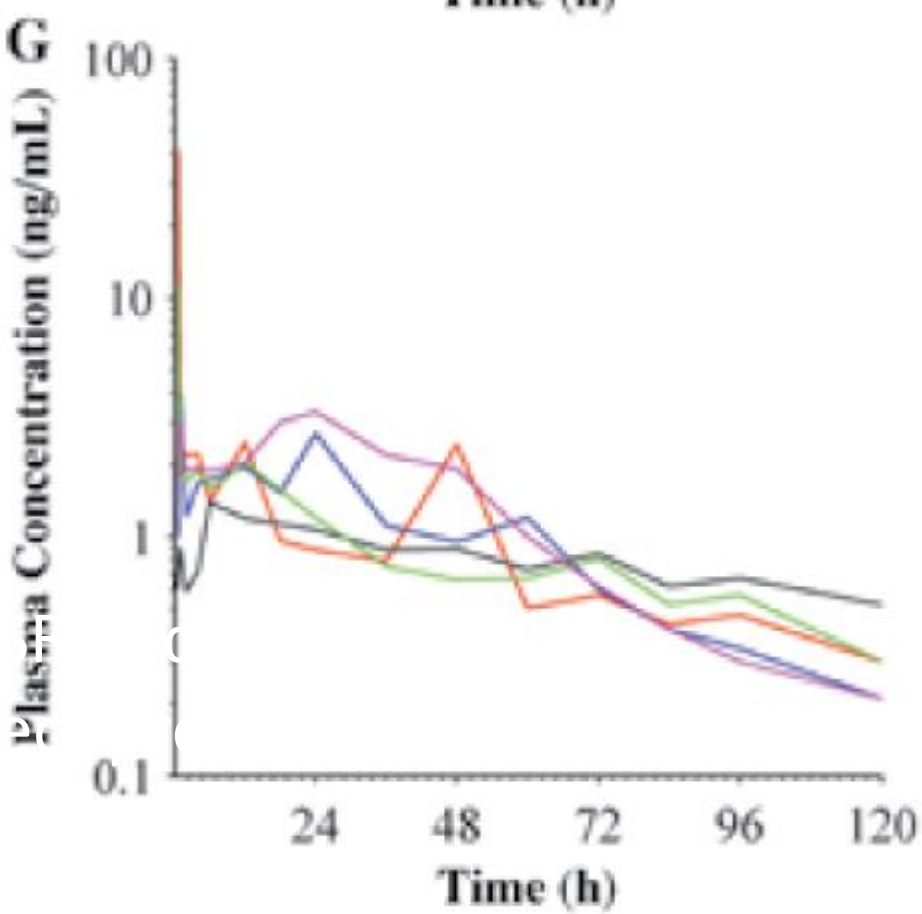


Foley, 2011

Buprenorphine SR

Nunamaker, 2013





0.01 mg/kg IM Bup HCl

0.2-mg/kg SC BupSR

Recommendations for Sustained Release Buprenorphine

- Appears to be efficacious in rats.
- More efficacy studies to verify plasma levels correlate to adequate pain relief in veterinary patients.
- Need to consider:
  - frequency of adverse reactions
  - inability to reverse
  - subsequent pain assessment following injection (i.e. not a “1 and done” analgesic)

Tramadol

- Not federally controlled
  - DEA has proposal to change to schedule IV.
- Some states currently list as schedule IV.
  - Arkansas, Illinois, Kentucky, Mississippi, New Mexico, New York, North Dakota, Oklahoma, Tennessee, and Wyoming.

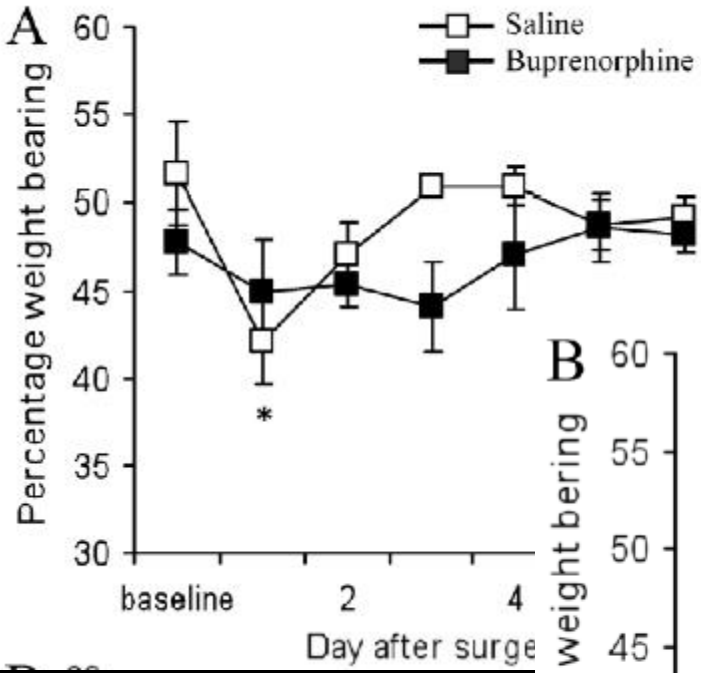
http://www.deadiversion.usdoj.gov/fed_regs/rules/2013/fr1104.htm

Tramadol

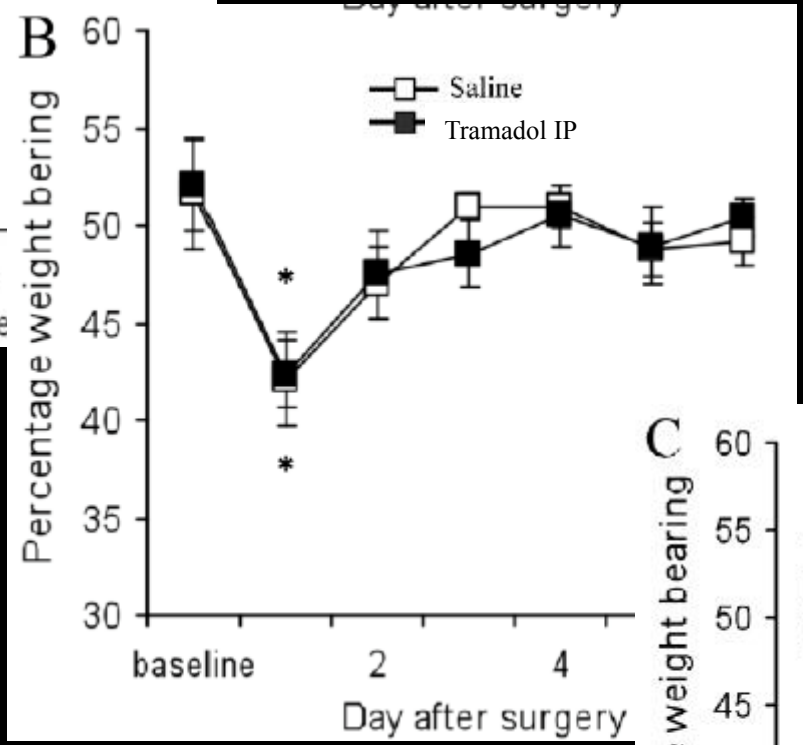
- Mice: (Koutroli, 2014; Rätsep, 2013; Hugunin, 2010)
  - Meloxicam out-performed in efficacy studies.
  - No clear evidence for Tramadol's analgesic efficacy.
  - Disrupted circadian rhythm, food consumption, activity and, increased weight loss.
  - Increased deaths in high dose group after CLP surgery.

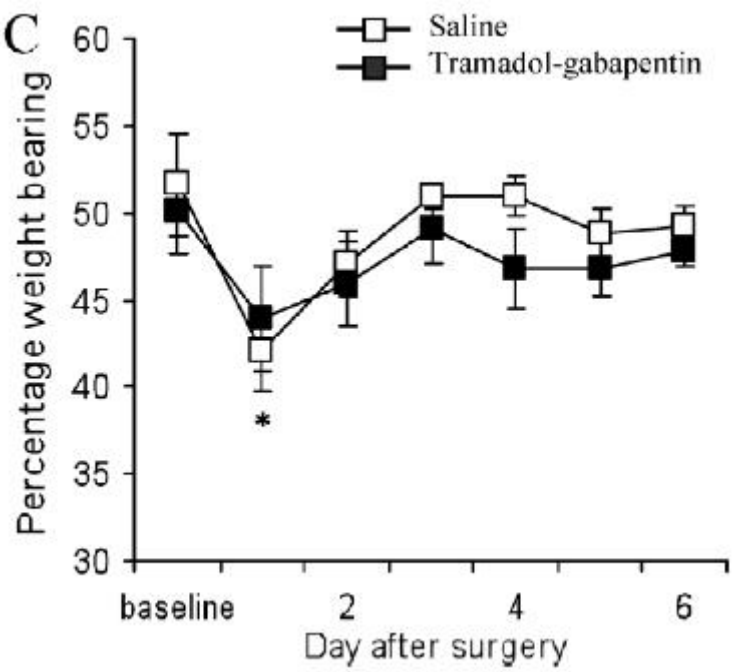
Tramadol

- Rats: (Ciuffreda, 2014; Kimura, 2012; McKeon, 2011; Zegre Cannon, 2011)
  - All doses and routes (IP, intrathecal) produced analgesic effect in a dose-dependent manner.
  - Post-op wheel running returned to baseline levels one day earlier.
  - Compared to carprofen:
    - No significant differences in fecal corticosterone, body weight, consumption, or clinical observations .
    - More sedating.
  - Compared to buprenorphine:
    - Provided insufficient analgesia for incisional pain.
  - Some improved efficacy when co-administered with gabapentin or carprofen.



*Significant ($P < 0.05$) difference compared with baseline value for group.





McKeon, 2011

Recommendations for Tramadol

- Mice:
  - No clear evidence of efficacy
  - Multiple side effects shown
- Rats:
  - Some analgesic efficacy evidence
  - Given alone, provides inferior analgesia compared to other choices (Carprofen, Buprenorphine, co-administered with Carprofen or Gabapentin)

Hot Topics in Analgesia

- Pain Assessment
- Non-pharmacologic Analgesia
- Oral Dosing of Analgesia
- Sustained Release Analgesia
- Tramadol
- Multimodal Analgesia
- Transdermal Analgesia
- Regional Analgesia

Multimodal Analgesia

- Tramadol & Carprofen
- Buprenorphine & Carprofen
- Buprenorphine & Meloxicam
- Tramadol & Gabapentin

Tramadol & Carprofen

Rats: (Ciuffreda, 2014; Zegre Cannon, 2011)

- 80% rats treated with multimodal determined to be less stressed after surgery compared to 15-20% of rats treated with only one of the analgesics.
- Locomotor activity was similar before and after surgery in rats treated with carprofen or multimodal combination.

Tramadol & Carprofen

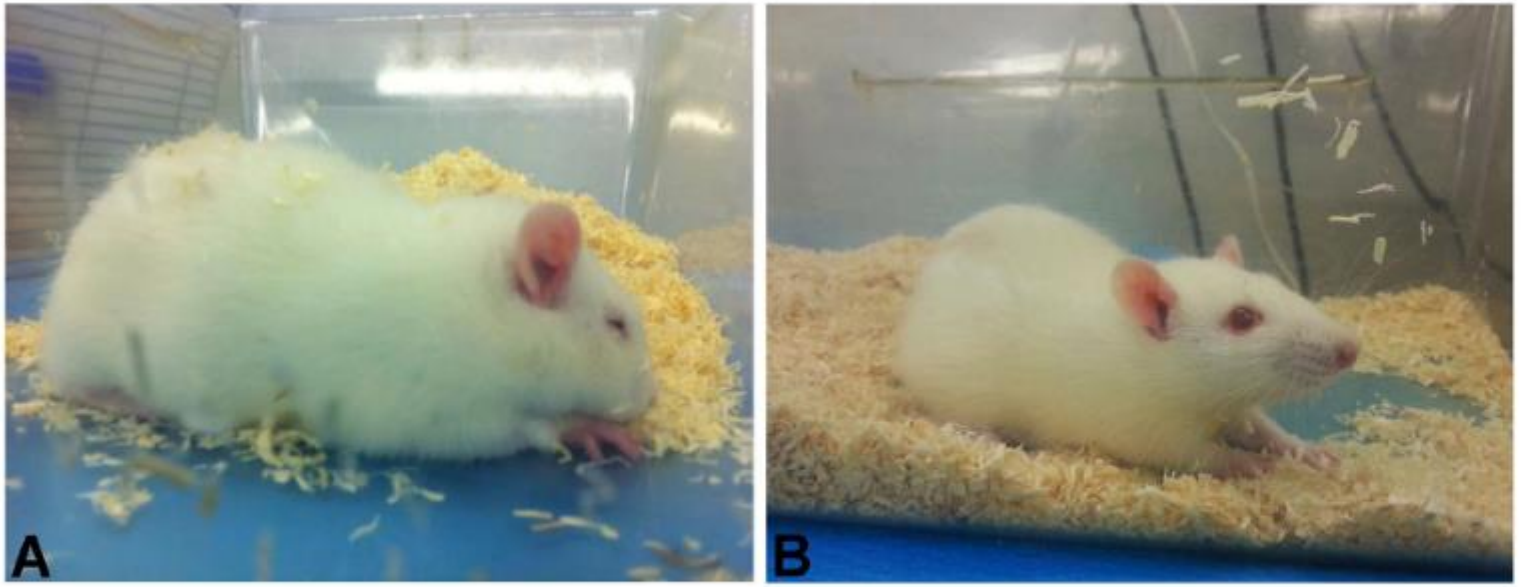


Figure 5. Example of stress behavior. (**A**) Carprofen treated rat exhibiting distress reactions 1 h after surgery. (**B**) Carprofen+Tramadol treated rat showing normal behavior 1 h after surgery.
doi:10.1371/journal.pone.0095913.g005

Ciuffreda, 2014

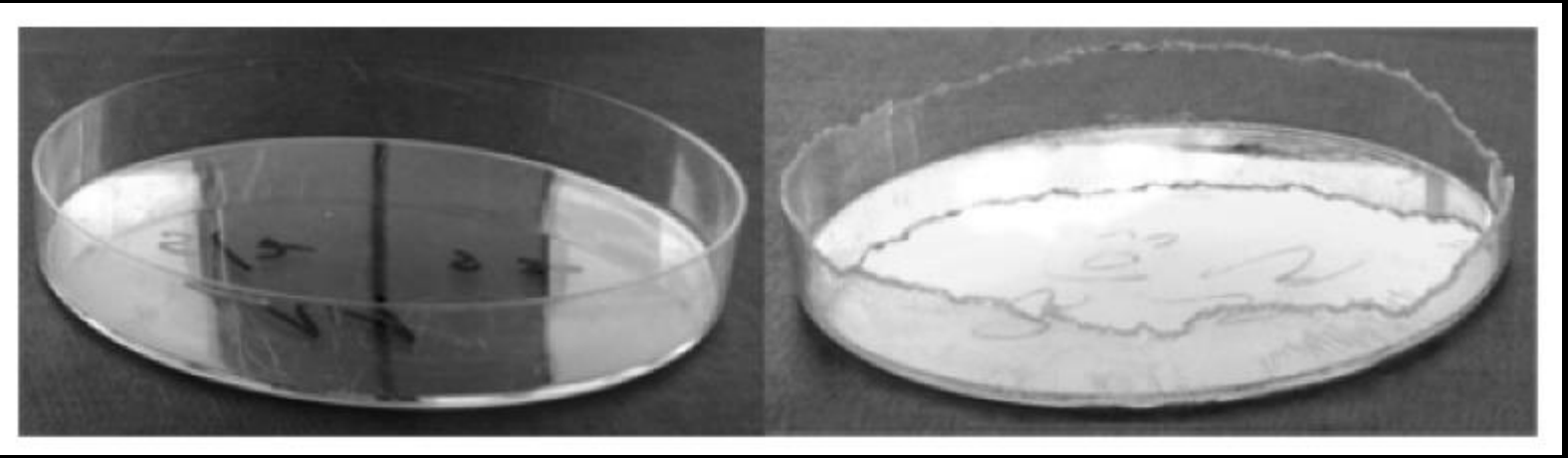
Buprenorphine & Carprofen

Mice: (Parker, 2011; Adamson, 2010)

- Multimodal analgesia had no significant positive or negative effect on the success of blastocyst transfer.
- The parameters used did not indicate either agent alone or combined improved recovery as compared with that of saline-treated mice.

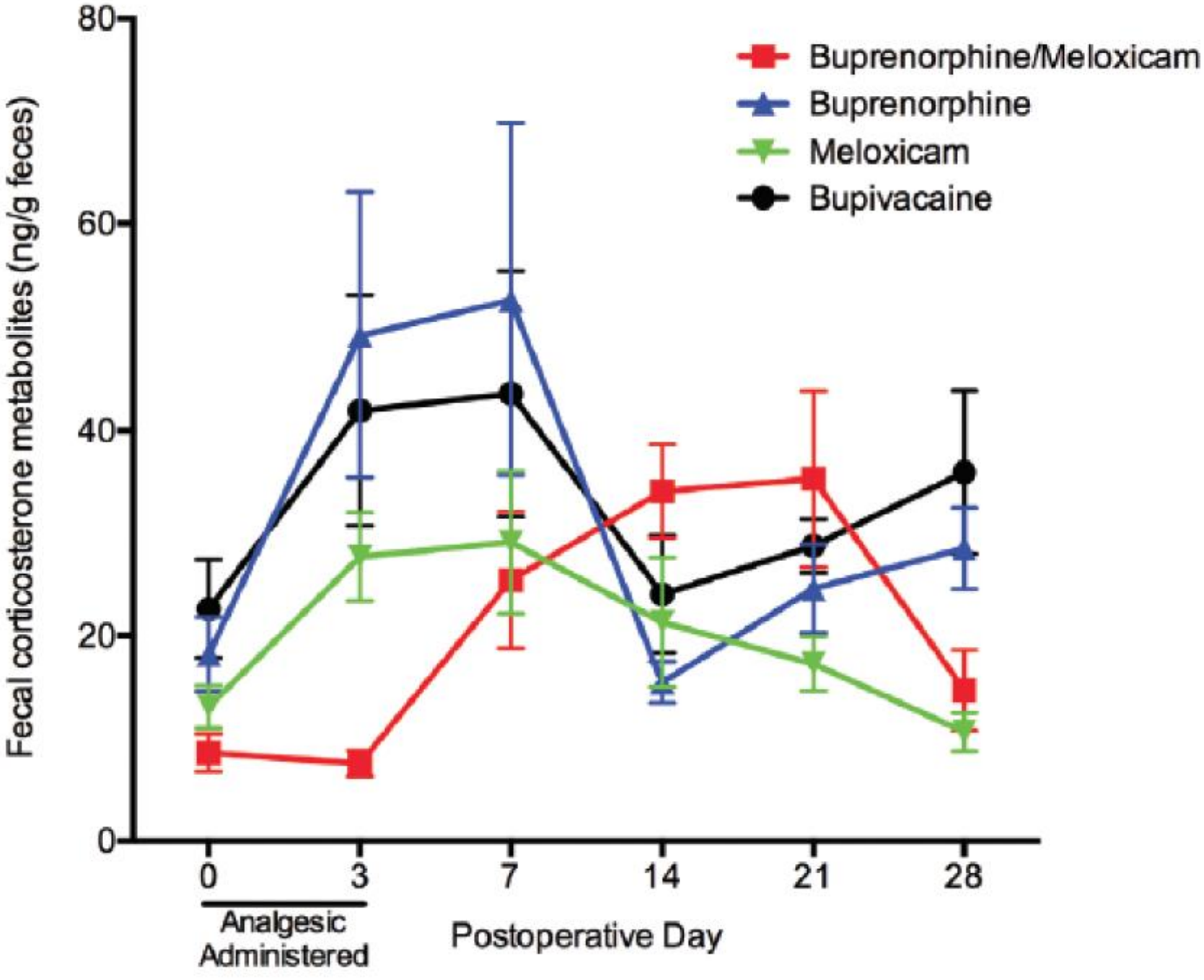
Buprenorphine & Meloxicam

- Rats: (Schaap, 2012)
  - No significant differences in body weight or food intake between TID and BID Buprenorphine groups.
  - TID group did exhibit increased gnawing behavior however, no clinical sequelae reported.



BID Buprenorphine

TID Buprenorphine


Buprenorphine/Meloxicam
Buprenorphine
Meloxicam
Bupivacaine
Fecal corticosterone metabolites (ng/g feces)
80
60
40
20
0
0
3
7
14
21
28
Analgesic Administered
Postoperative Day

Tramadol and Gabapentin

- Rats (McKeon 2011; Narai 2012)
  - Ameliorated thermal hyperalgesia and weight-bearing deficits less effectively than did buprenorphine alone.
  - Intrathecal Gabapentin (alone) attenuated postoperative mechanical hyperalgesia for 7 days

Multimodal Analgesia *Recommendations*

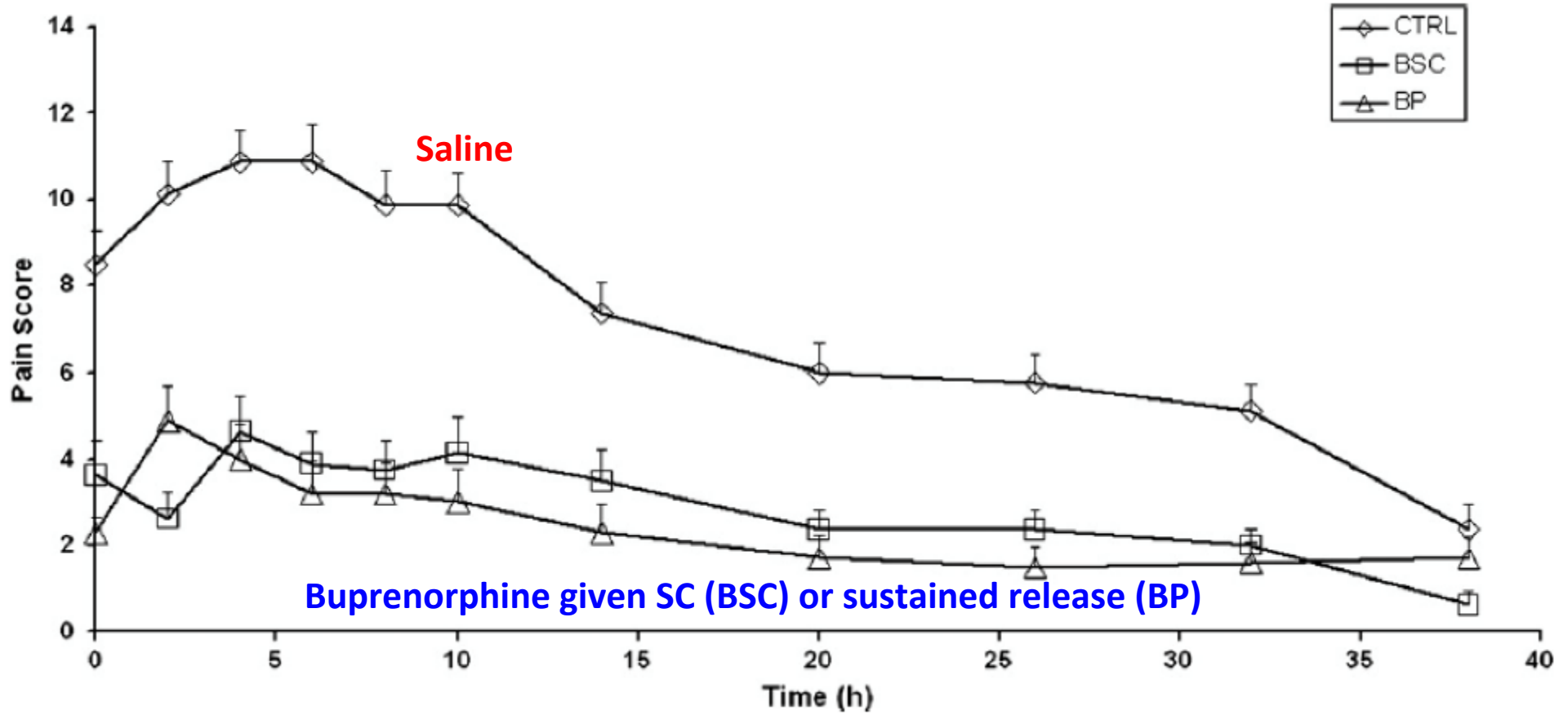
- Tramadol & Carprofen
  - Evidence for analgesic efficacy in rats
- Buprenorphine & Carprofen
  - Questionable analgesic efficacy reported in mice but neutral impact on embryo transfer success.
  - Need more peer reviewed studies to support efficacy.
- Buprenorphine & Meloxicam
  - Neutral to positive evidence for analgesic efficacy in rats and rabbits.
- Gabapentin & Tramadol
  - Some evidence of efficacy in rats
  - Did not outperform other analgesic options such as buprenorphine.

Transdermal Analgesia

- Buprenorphine
- Fentanyl

Buprenorphine patch

- Dogs: (Moll, 2011, Piepera, 2011)
  - Equianalgesic to SC Buprenorphine for controlling clinical post-spay pain.
  - Thermal antinociception achieved beyond 36 h.
  - Peak concentration was 1.54 ng/mL 60 h after application.
  - Patch failed to work at all in 30% of the dogs.



Pain Score consisted composite of categories: Physiologic, Response to Palpation, Activity, Mentation, Posture, Vocalization

Moll, 2011

Fentanyl Patch

- Dogs (Linton 2012)
  - Investigational formulation
  - administered 2–4 h prior to surgery
  - provides analgesia that is non-inferior to repeated injections of buprenorphine over 4 days
- Pigs (Malavasi, 2006)
  - In combination with epidural resulted in earlier return to normal activity levels and an immediate weight gain after surgery.

Table 5. Adverse event rate for TFS- and buprenorphine-treated dogs from the time of first treatment on Day 0 through Day 4 with an incidence of event rate of ≥1% in either treatment group

	TFS (N = 223)	Buprenorphine (N = 222)
Category	n (%)	n (%)
Emesis	12 (5.4)	11 (5.0)
Diarrhea	9 (4)	9 (4.1)
Sedation	8 (3.6)	3 (4.1)
Anorexia	7 (3.1)	3 (1.4)
Hypersalivation	4 (1.8)	1 (0.5)
Ataxia	4 (1.8)	0 (0.0)
Bradycardia	3 (1.3)	5 (2.3)
Conjunctivitis	3 (1.3)	4 (1.8)
Hypothermia	3 (1.3)	4 (1.8)
Tachycardia	1 (0.4)	3 (1.4)

TFS, transdermal fentanyl solution.

Linton 2012

Buprenorphine – 0.02 mg/kg IM, every 6 hrs

Fentanyl Patch

- Rabbits (Foley, 2001)
  - Plasma concentration reached 1.11ng/ml by 24 h and remained high until 72 hours.
  - Hair should be clipped and not removed with depilatory cream.
    - Use of cream resulted in increased rate of absorption leading to sedation and lack of sustained plasma concentrations.

Hair clipped prior to patch application

Depilatory cream used to remove hair

If hair follicles are in anagen phase at the time of patch application, rapid hair regrowth poses a problem with drug absorption.

Foley, 2001

Transdermal Analgesia *Recommendations*

- Buprenorphine:
  - Analgesic for at least 1.5 days, possibly as long as 5 days in dogs.
  - High failure rate (30%)
- Fentanyl
  - Analgesic in dogs, pigs and rabbits
  - Careful prep of skin prior to placement

Medicine Center

- Medicine
- Internal Medicine
- Animal Welfare
- Behavior
- Dentistry
- Dermatology
- Equine
- Exotics
- Feline
- Food Animals
- Ophthalmology
- Parasitology
- Surgery
- Forms

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How to make a soaker-type catheter

Jan 1, 2009
By: Christine Egger, DVM, MVSc, DACVA, Lydia Love, DVM
VETERINARY MEDICINE

The following materials are needed:

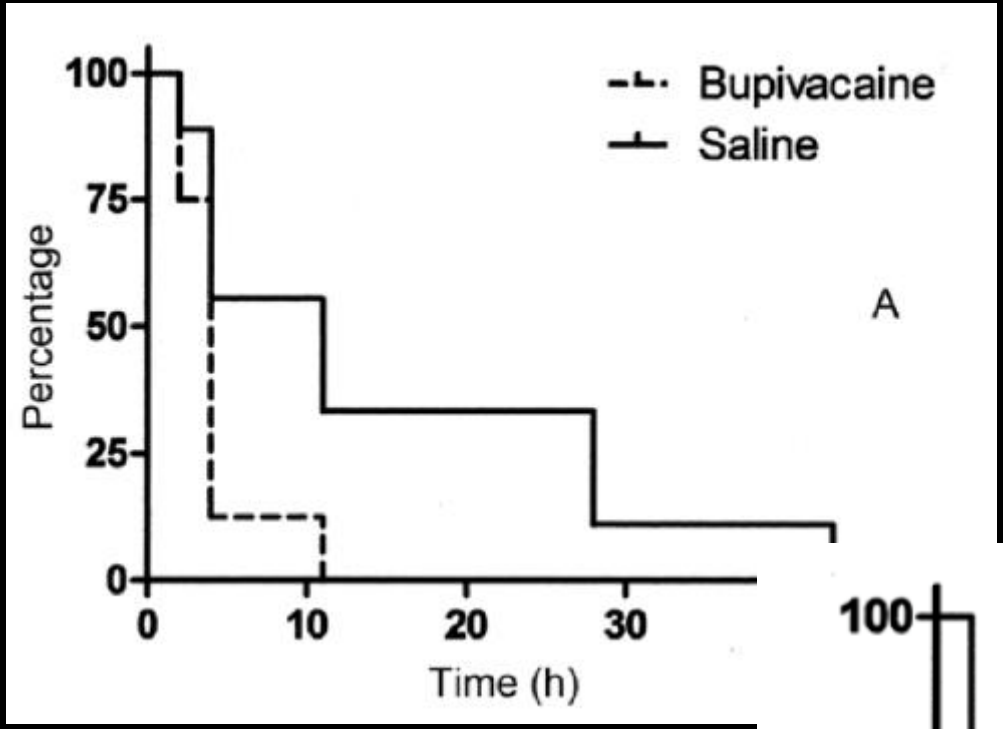
- 3.5-, 5-, or 8-F red rubber catheter
- Sterile scissors (Mayo/sharp-blunt)
- Sterile Halsted mosquito forceps
- Heat source, such as a cigarette lighter
- Sterile 3-ml syringe
- 27-ga needle (found on insulin syringes)
- Sterile infusion plug
- Sterile gloves
- Sterile drape

Regional Analgesia

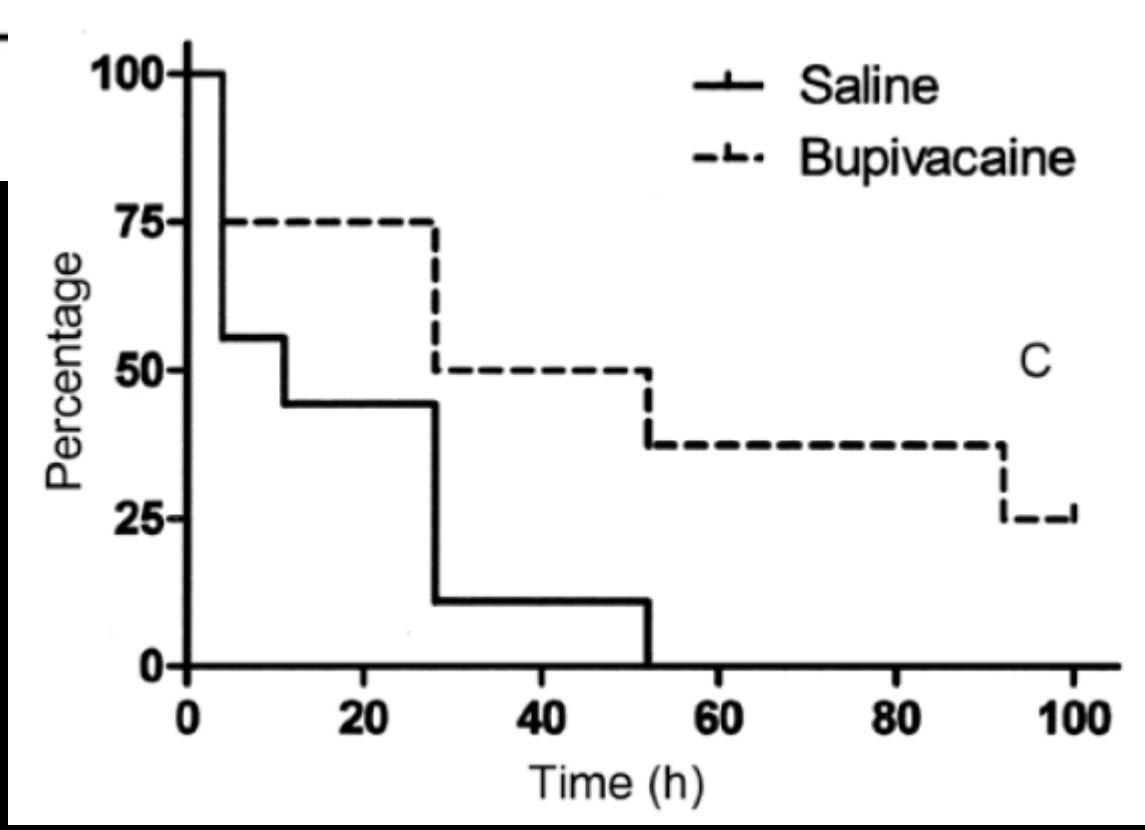
- Sheep: (Wagner, 2014; Carney, 2009; Lofgren 2014- clinical obs.)
  - Soaker catheter: sheep post thoracotomy improved, require less rescue analgesia (not published)
  - Multi-modal analgesia, including a diffusion catheter, contributed significantly to sheep recovery from ventricular assist device placement
  - Single Block: Aside from improved movement 2 h after the procedure, there were no significant differences between sheep that received blocks from controls

Regional Analgesia

- Pigs: ultrasound guided placement of infusion catheter at time of surgery – femoral fracture (Royal, 2013)
  - Lower subjective pain scores than did control animals
  - Shorter latency to return to eating after surgery and required less rescue analgesia than controls.



Time to first feed after femoral fracture surgery in pigs



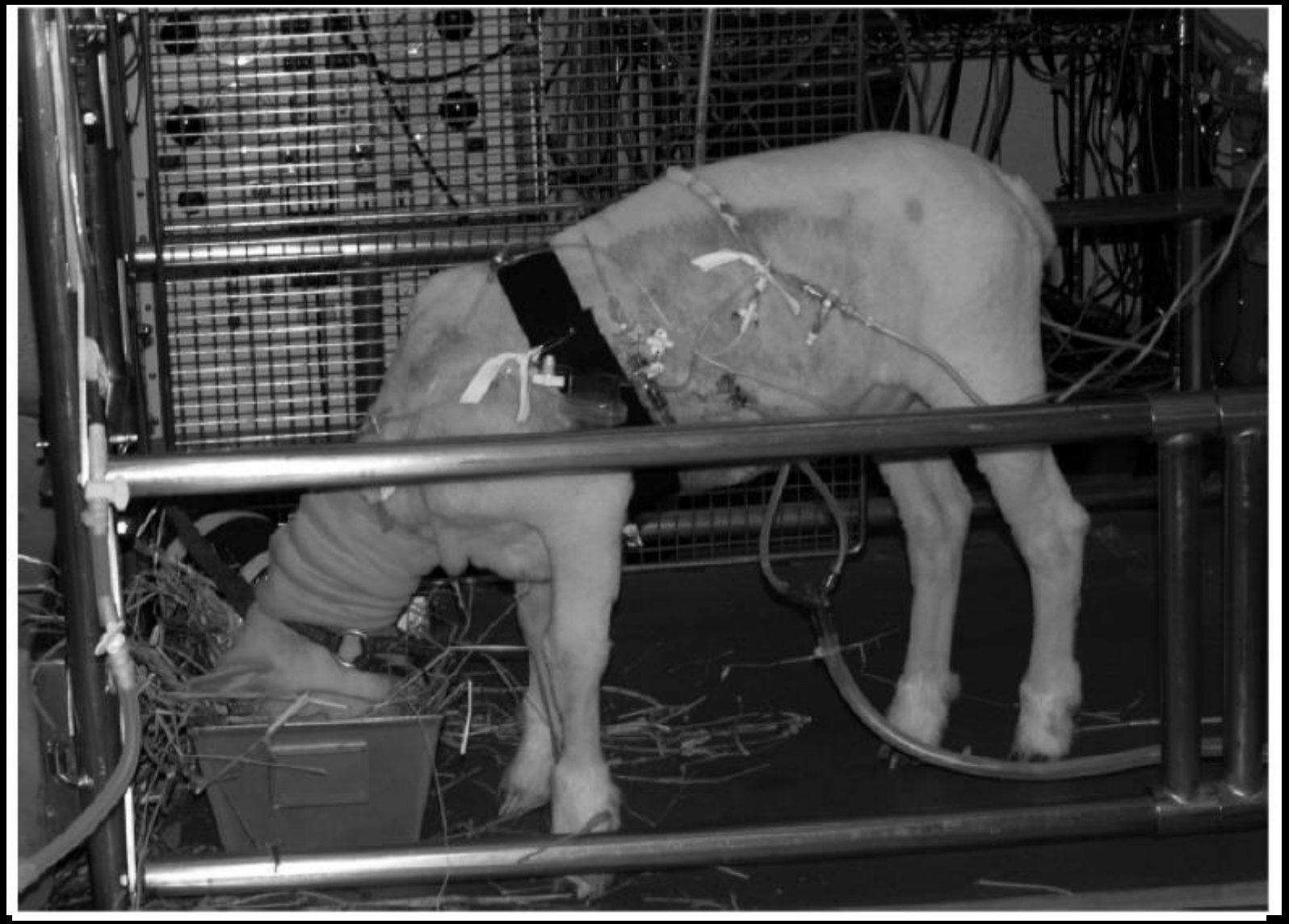
Time to needing rescue analgesia

Royal 2013

Regional Analgesia

- Dogs, Cats, Goats (Abelson, 2009)
  - Wound soaker catheters remained in place for 1.6 days
  - Cat and goats received intermittent bupivacaine boluses every 6 hours
  - Dogs received continuous lidocaine infusions.
  - Complication and infection rates equivalent to historical control cases.
- Ferrets: (Eschar, 2010)
  - Epidural used successfully to treat clinical post-operative pain.

Wound Soaker Catheters



(Ashley, 2009)

Regional Analgesia *Recommendations*

- Efficacy and benefit demonstrated for multiple species.
- Commercially available and can make own – perform equally well.
- Low infusion speeds with CRI can create uneven distribution of local anesthetic, resulting in inconsistent pain relief.
- Intermittent boluses of local anesthetics may be more effective than CRI. (Hansen, 2013)

Hot Topics in Analgesia

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Thank you!