Refinement of animal models of pain

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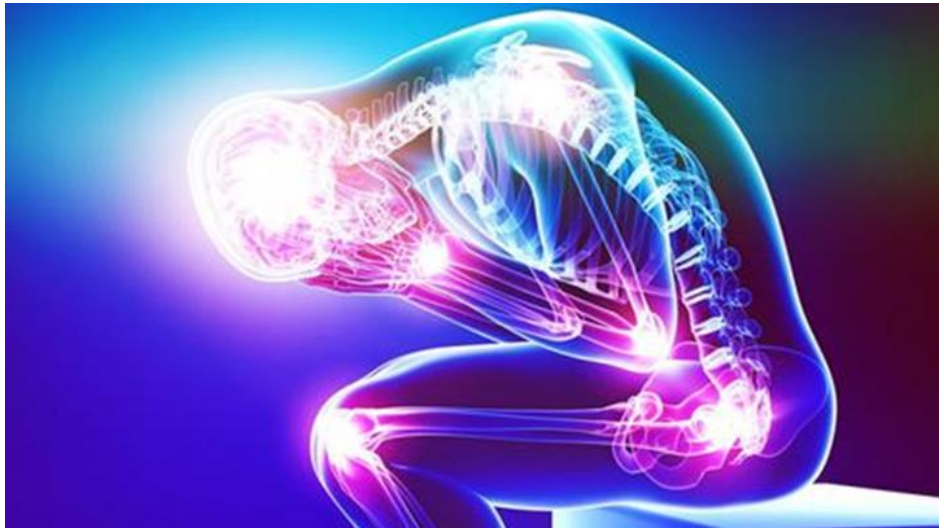
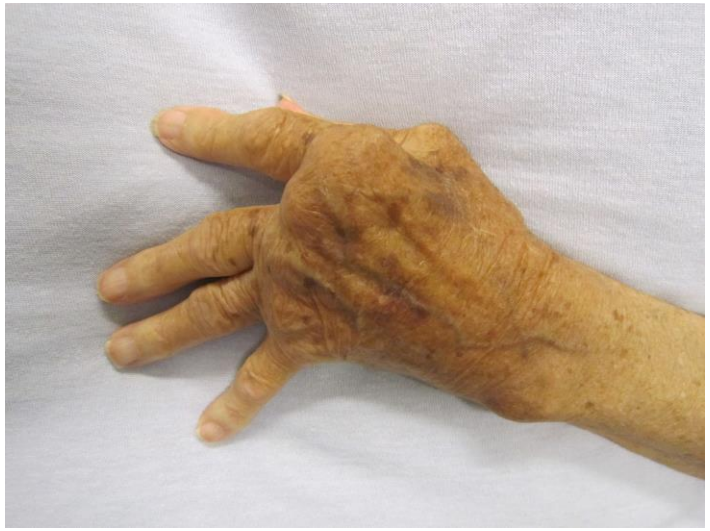
Background

- Painful conditions such as neuropathic pain or rheumatoid arthritis are severe clinical problem causing substantial suffering among humans (and animals)
- The treatments available as of today are for from sufficient – more potent and more effective drugs remain to be developed





Background

- Despite the emergence of non-animal models for studying human diseases, we doubtlessly need *in vivo* studies on animals to study disease progression and treatment in a foreseeable future
- This includes animal models of neuropathic pain, rheumatoid arthritis and other painful conditions
- Animal models of painful conditions are indeed problematic from a welfare perspective, since it is necessary to inflict painful stimuli or prolonged painful conditions on the animals

There is an obvious need for refinement

Three fundamental questions that are the basis of our research

1. Is there any avoidable element of pain in animal pain models (pain that is not related to the relevant test parameters)?
2. If so, can these elements of pain be avoided, and what analgesic regimen should be applied to give adequate pain relief while having no unwanted effect on the model?
3. Are there other means of improving technical aspects of the model that may enhance the welfare of the animals without adverse effect on the model?

Neuropathic pain models

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PLOS ONE

RESEARCH ARTICLE

Is there a reasonable excuse for not providing post-operative analgesia when using animal models of peripheral neuropathic pain for research purposes?

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Table 1. Treatment- and non-operated control-groups.

Group	Analgesic/dose	Administration	Treatment timing [1]	Abbreviation	Coverage / hours	N	N, end
A	Control (minimally handled and not operated)	-	-	Control	-	18	18
B	Control + von Frey tested (not operated)	-	-	Control + VF	-	14	14
C	Vehicle (saline)	s.c.	During anesthesia, prior to incision	Vehicle, s.c.	-	30	30
D	Buprenorphine, 0.1 mg/kg	s.c.	During anesthesia, prior to incision	Bup. s.c. 8h	8	30	30
E	Buprenorphine, 0.1 mg/kg	s.c.	During anesthesia, prior to incision + every 8 h	Bup. s.c. 72h	72	12	12
F	Buprenorphine, 1.0 mg/kg	Nutella/p.o.	45min prior to anesthesia	Bup. p.o. 8h	8	12	12
G	Buprenorphine, 1.0 mg/kg	Nutella/p.o.	45min prior to anesthesia + every 8 h	Bup. p.o. 72h	72	14	13*
H	Carprofen, 5.0 mg/kg	s.c.	During anesthesia, prior to incision	Carprofen, 24h	24	12	12
I	Carprofen, 5.0 mg/kg	s.c.	During anesthesia, prior to incision + every 24h	Carprofen, 72h	72	12	11**
J	Lidocaine 10 mg/Bupivacaine 2.5 mg, 1:1	Local	During anesthesia, post incision.	Lido/bupi	2–3	12	12
K	**High dose combination:** Carprofen, 5 mg/kg. Buprenorphine 0.1 mg/kg. Lidocaine10 mg/ bupivacaine2.5 mg– 1:1	s.c./local	During anesthesia, prior to incision + local post incision.	High combination	72	18	12*, **
L	**Low dose combination:** Carprofen, 5mg/kg. Buprenorphine 0.05 mg/kg. Lidocaine10 mg/ bupivacaine2.5 mg– 1:1	s.c./Local	During anesthesia, prior to incision + local post incision.	Low combination	72	12	12

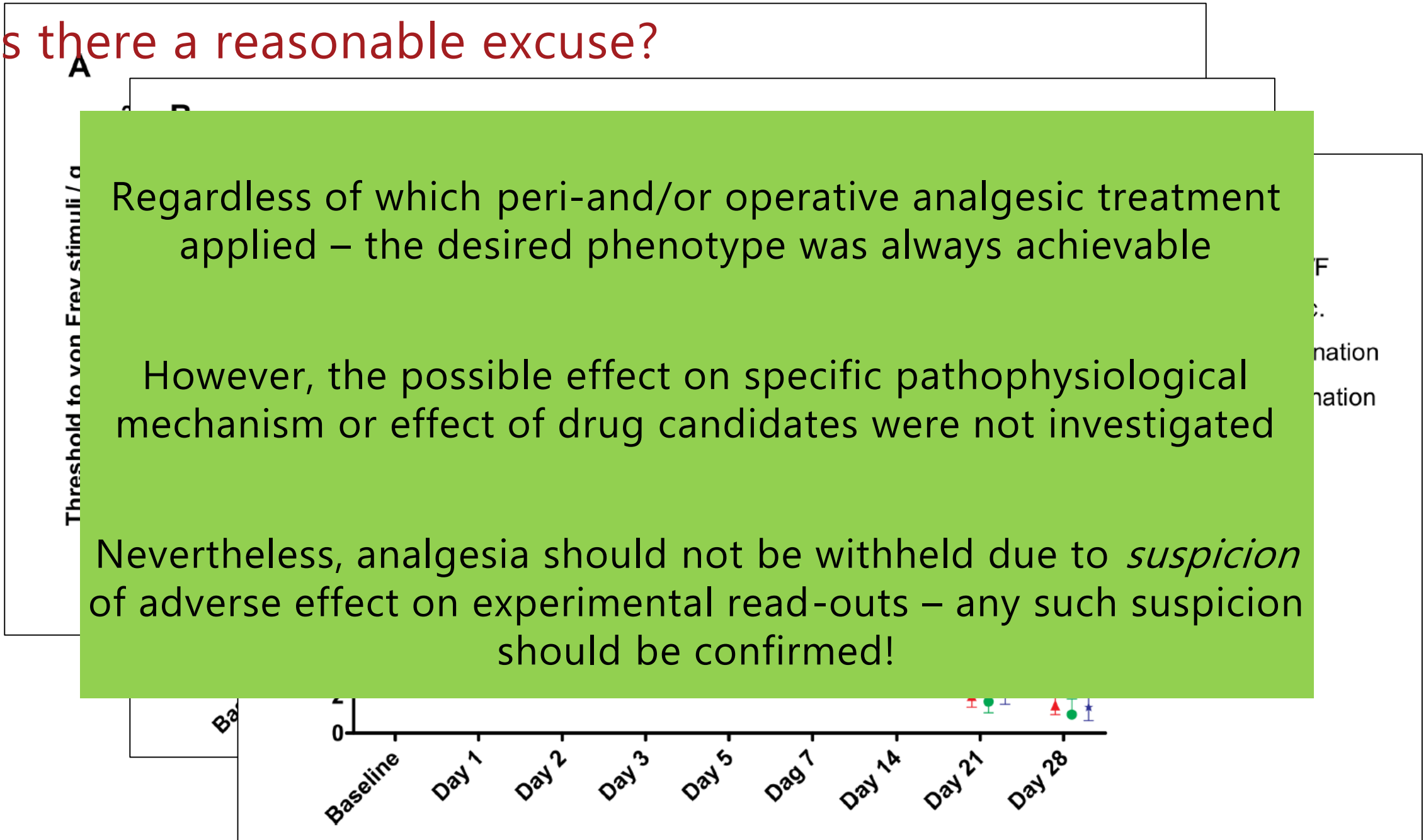
https://doi.org/10.1371/journal.pone.0188113

Is there a reasonable excuse?

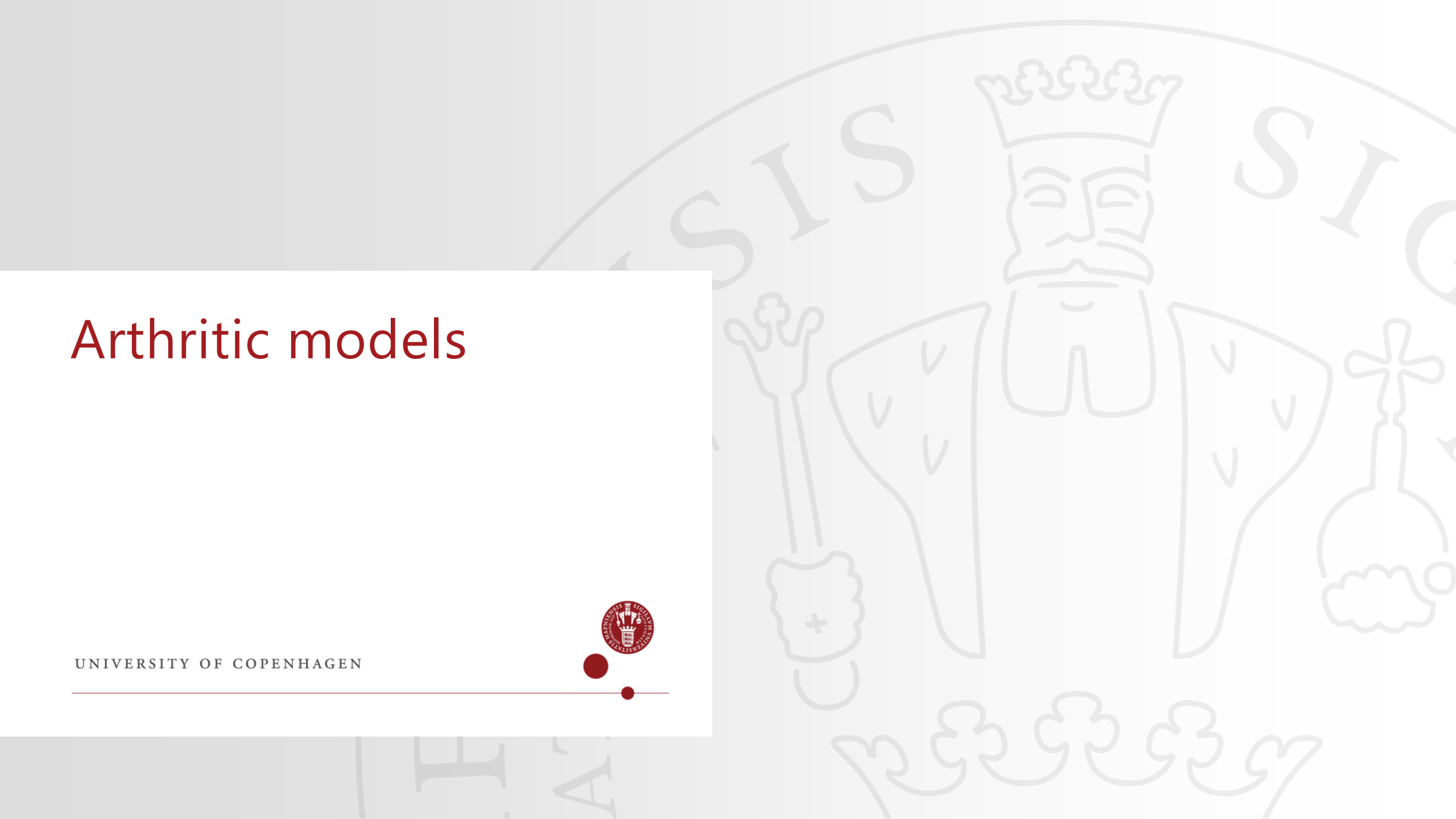
Regardless of which peri-and/or operative analgesic treatment applied – the desired phenotype was always achievable

However, the possible effect on specific pathophysiological mechanism or effect of drug candidates were not investigated

Nevertheless, analgesia should not be withheld due to *suspicion* of adverse effect on experimental read-outs – any such suspicion should be confirmed!



Arthritic models



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Where should we aim our refinement?

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Original scientific article

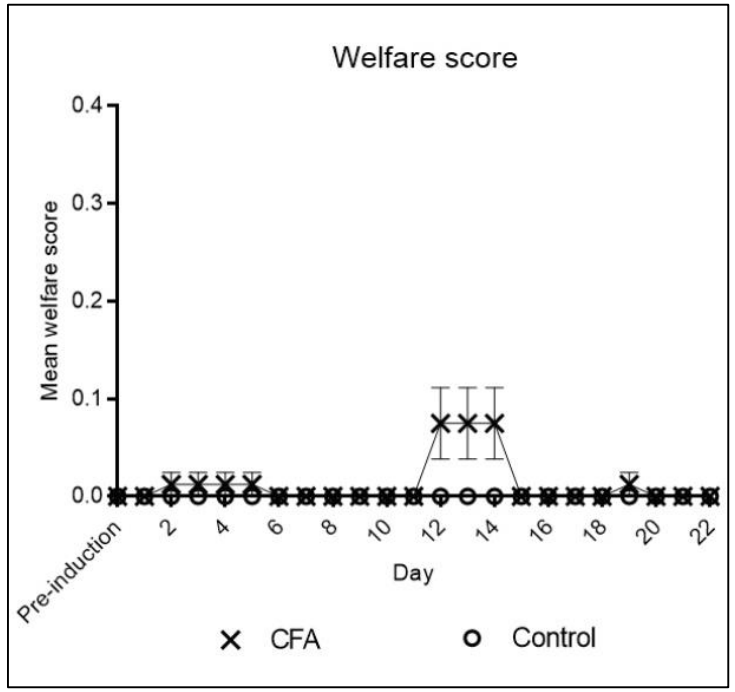
The adjuvant-induced rat model of monoarthritis: welfare implications and possible refinement strategies

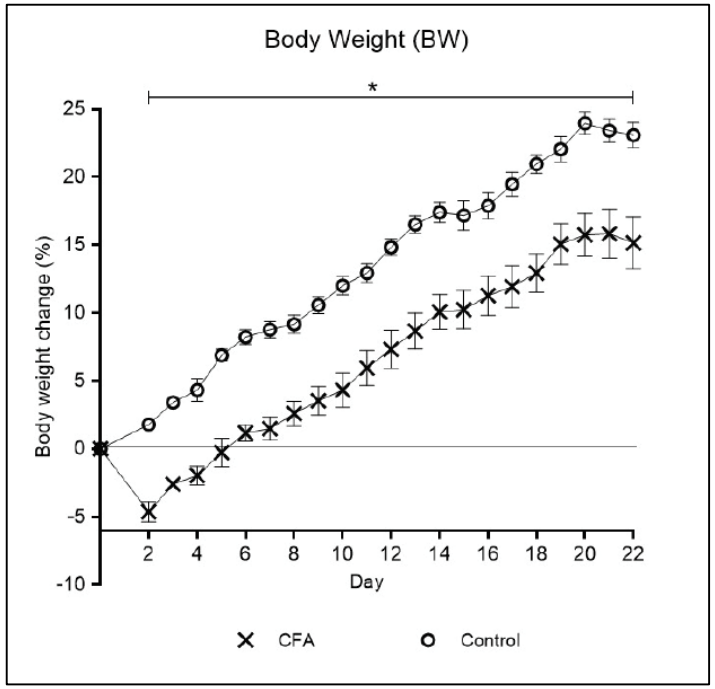
*By *Mie S. Berke and Klas S.P. Abelson*

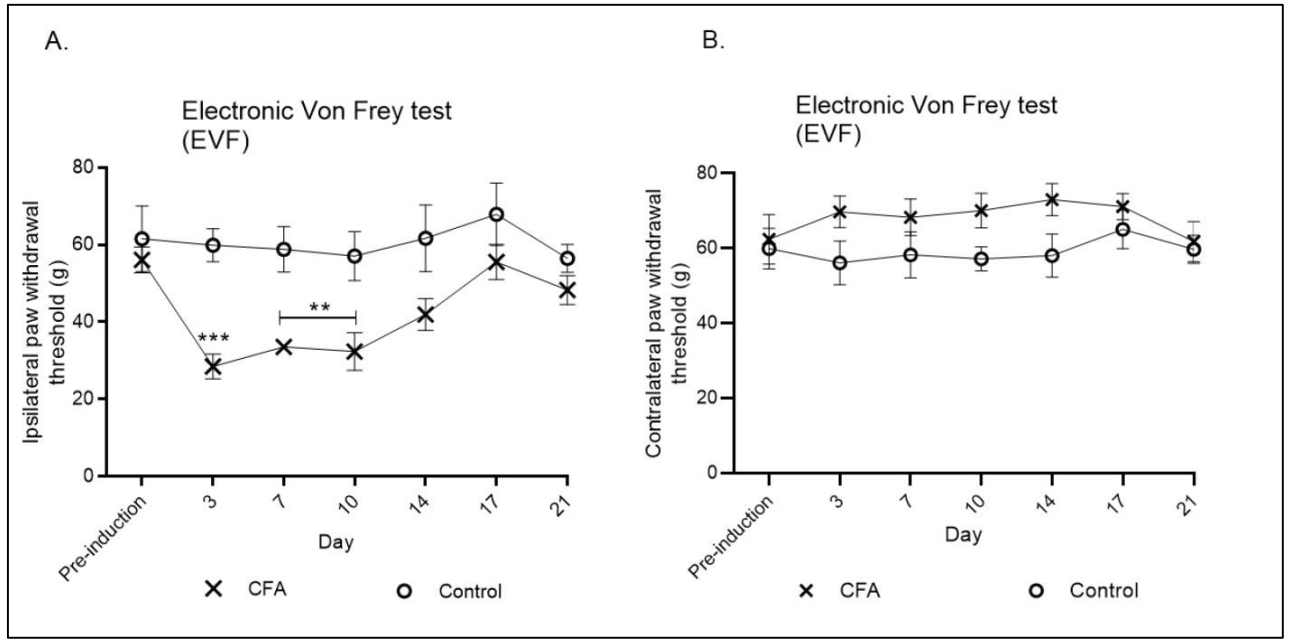
Department of Experimental Medicine, Faculty of Health and Medical Sciences, University of Copenhagen

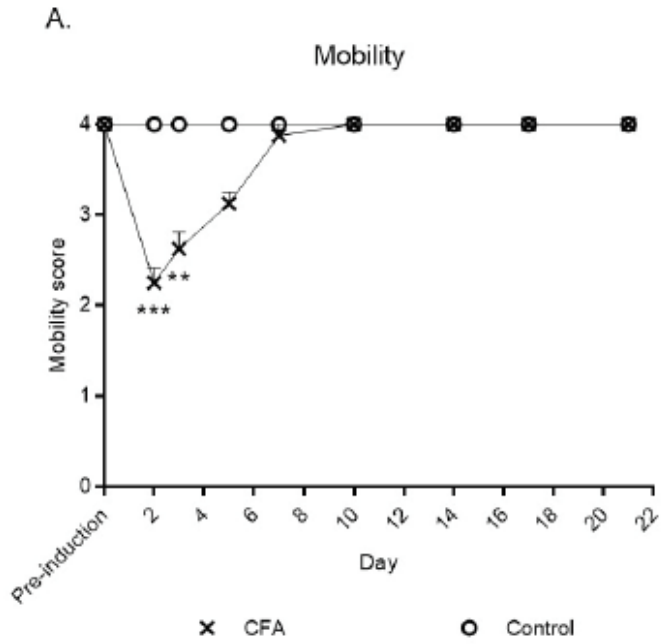
https://doi.org/10.23675/sjlas.v46i1.1046

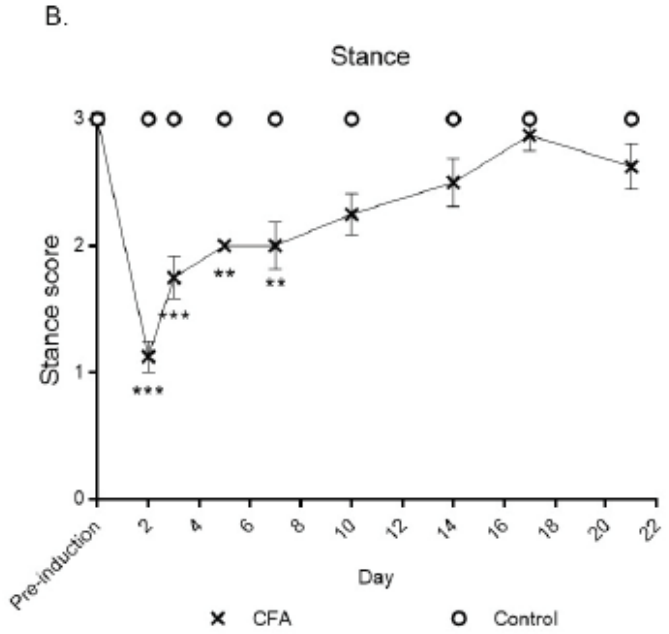
- Overall welfare is not severely affected (not close to predefined humane endpoints)
- But animals are indeed negatively affected, with body weight loss and significant pain
- In particular during the early phase of the experiment

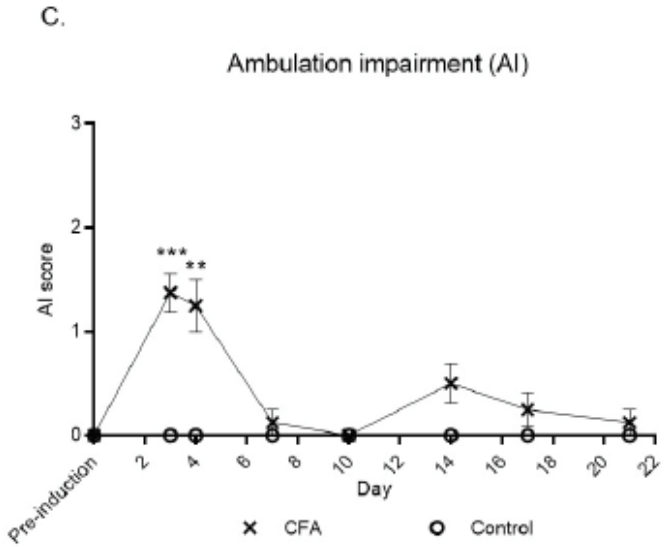


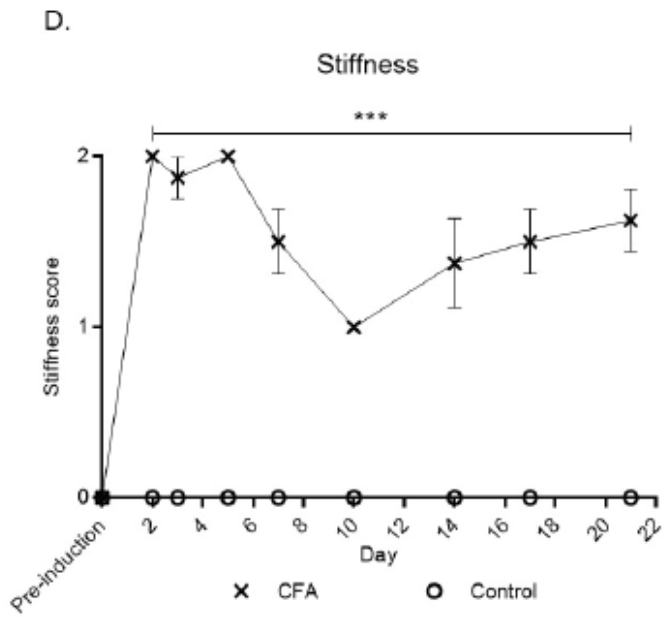












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- A-C only present in the early phase
- D-E throughout the whole experiment
- All animals developed pathological changes in the joints
- Pain in the early phase is avoidable?

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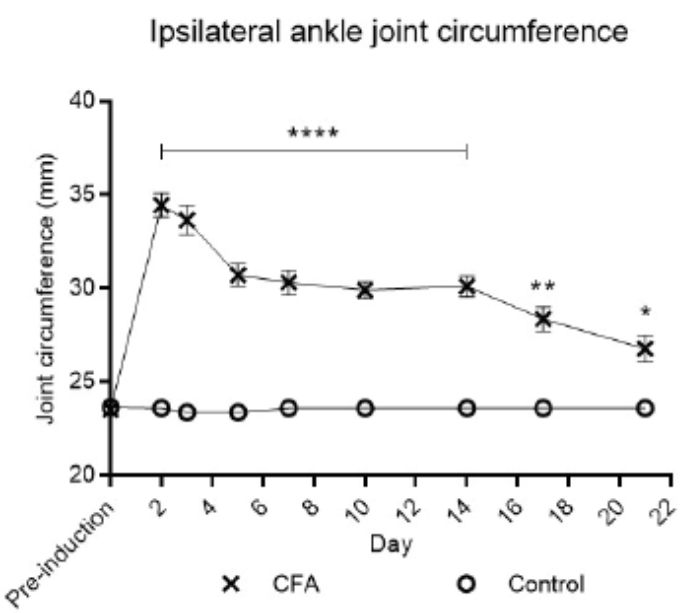
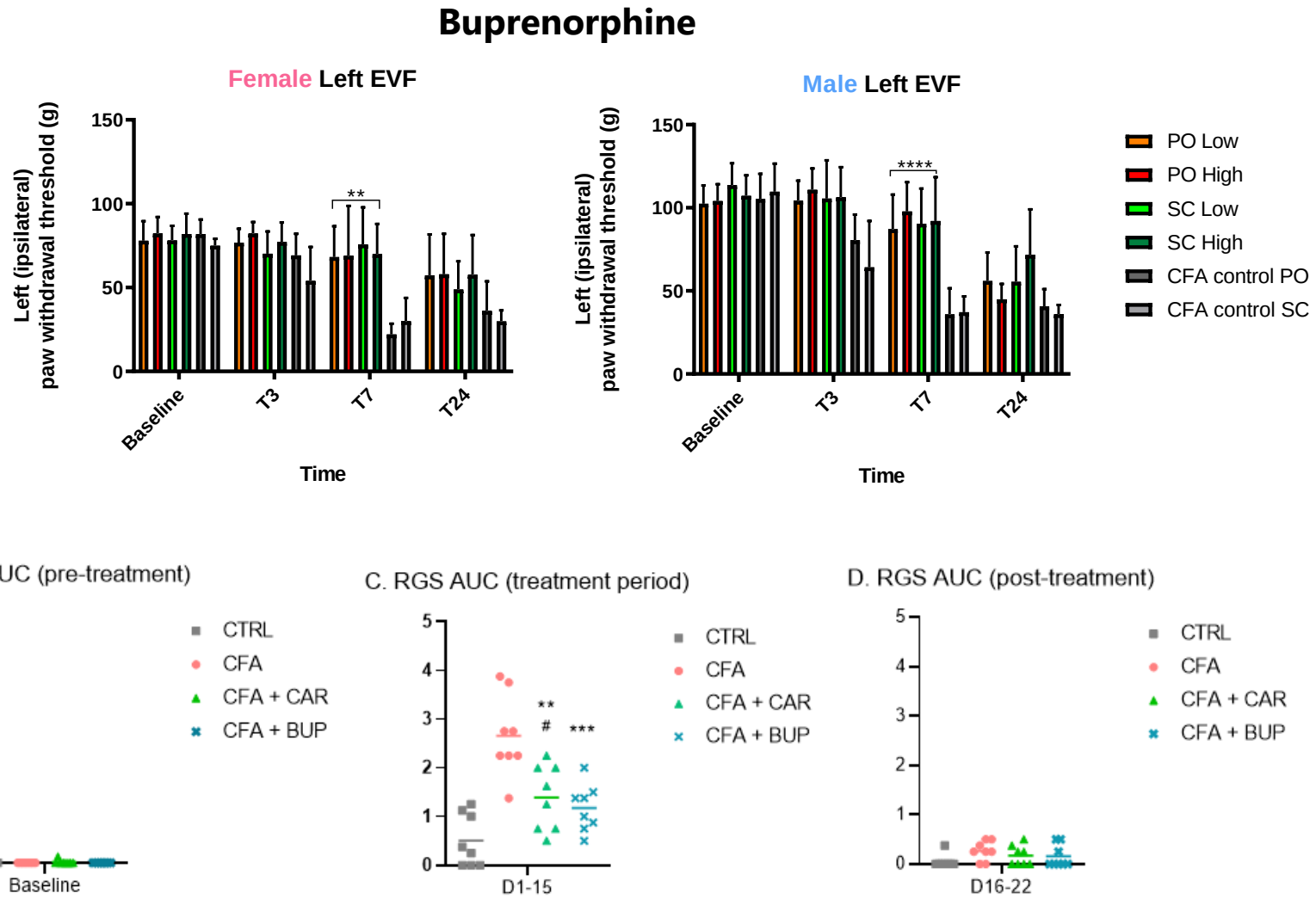


Follow up-studies

- Screening for relevant analgesic regimens and established the in the optimized arthritis model
- Refining and optimizing the rat model for monoarthitis, by increasing the success rate with induction and minimizing adverse effects on surrounding tissues, irrelevant to the arthritis

Screening for optimal analgesia – results at a glance

- Both buprenorphine (oral and parenteral) and transdermal fentanyl relieves pain in the early phase after induction
- None of the regimens seems to have any negative impact on the monoarthritic rat model
- Three manuscripts submitted or in preparation



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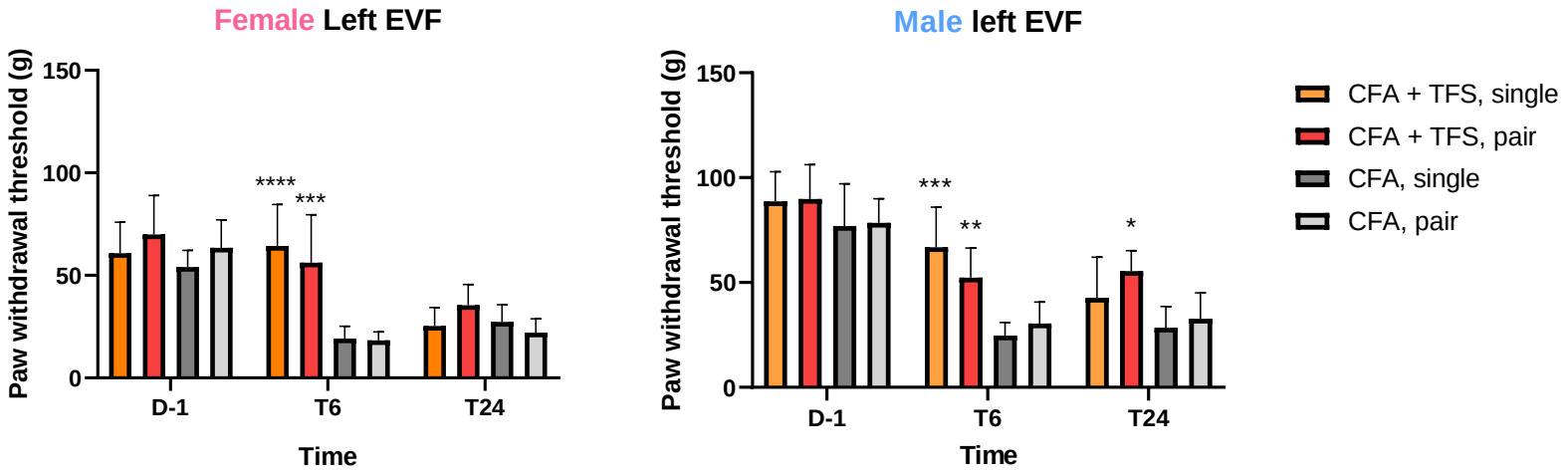
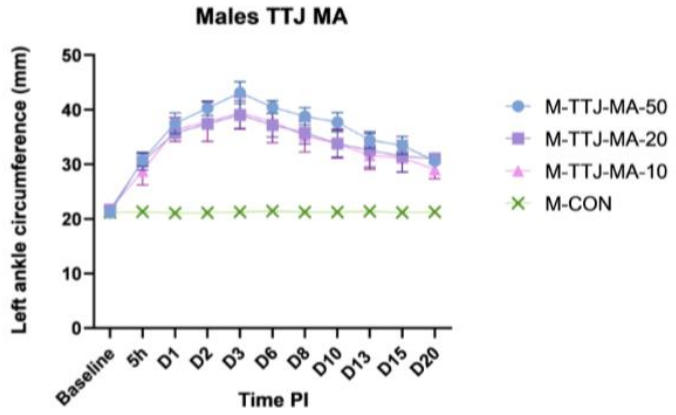
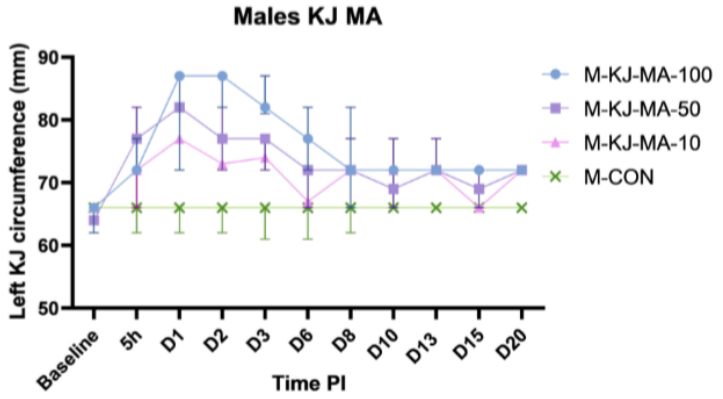
Transdermal fentanyl

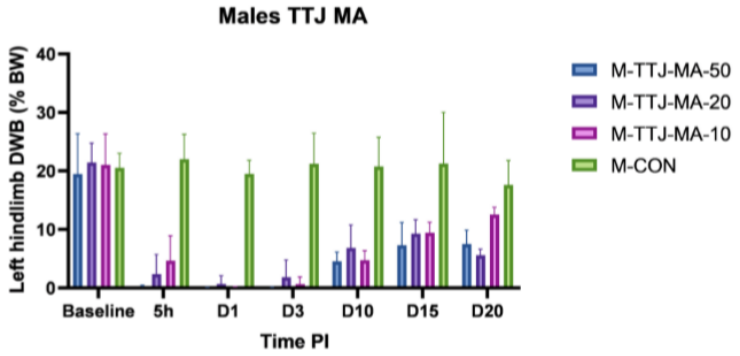


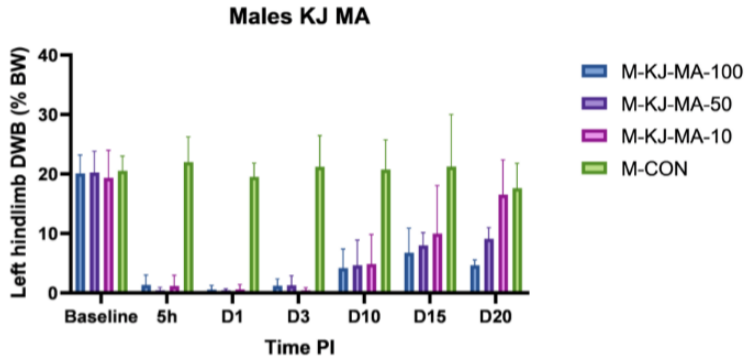
Improving the induction of the model – results at a glance

- Establishing the model by injection into the knee joint instead of the tibio-tarsal joint shows similar disease pattern
  - The knee joint is advantageous since risk of leakage into surrounding tissue is smaller
- The injection volume can be considerably reduced compared to standard volumes with similar disease pattern
  - Less adverse effects and less risk of leakage – refinement and improvement
- One manuscript in preparation
- Spin-off manuscripts most likely to come









Conclusions about arthritic models

- It is **possible to refine** the monoarthritic model
  - By technical improvements with alternative injection sites and injection volumes
  - By analgesic treatment
- Practically no adverse effect on model parameters
- Difficult to measure improved welfare

More research is needed (also in mice), and we've just started

Many thanks to those involved

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…and many more!