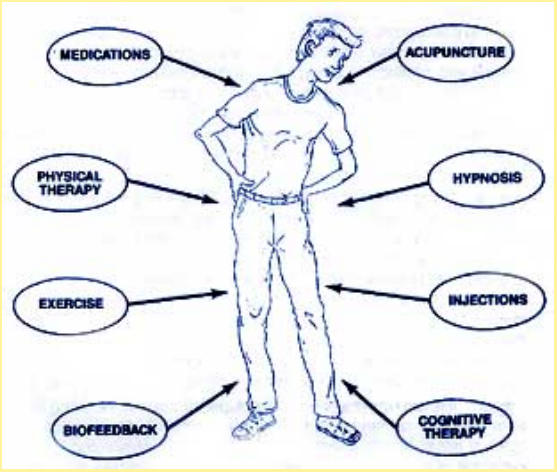
Animal Models and Translational Pain Research

International Society for Anaesthetic Pharmacology
2017

Boston, MA

Acute and chronic pain: options for treatment?



Many medicines, few cures
Benjamin Franklin

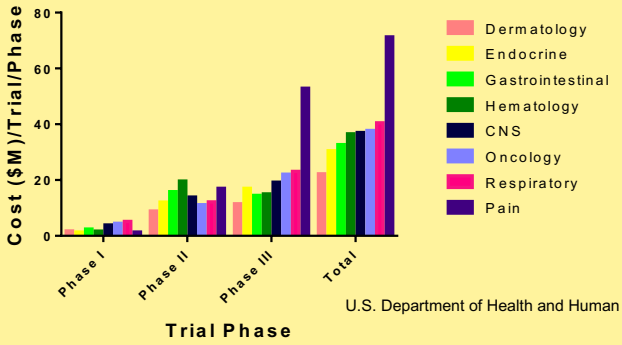
What has changed in 20 years?

1997	2017
NSAIDS	Similar (COX2)
Acetaminophen	Similar (IV)
Opioids	Similar (Formulations)
Antidepressants	Similar (More SNRI's)
Gabapentin	Similar (Pregabalin)
Tramadol	Similar (Tapentadol)
Capsaicin	Similar (Patch)
Lidocaine	Similar (Patch)
	Omega conotoxin
	Botulinum toxin
	Anti-NGF/Sativex/CGRP antag.

Trial Costs for Specific Therapeutic Areas

10.7% of analgesics entering Phase 1 trials are eventually approved*

Hay et al., Nat. Biotech., 2014

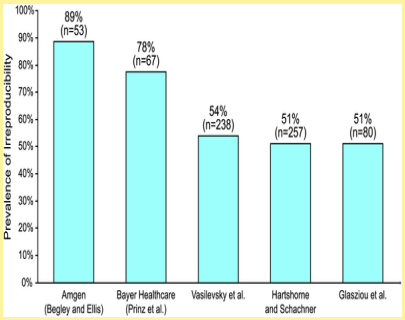


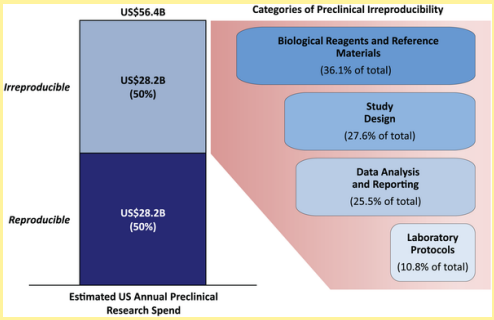
U.S. Department of Health and Human Services, 2014

Goal: Optimize preclinical testing to make translation to specific human pain states most likely.

The Reproducibility of Preclinical Testing

- If 50% of preclinical research is irreproducible, over $28B is wasted per year in the US alone.





Freedman et al. PLOS Biology, 2015

Reporting Guidelines

- Contributing problem: Failure to describe research methods and to report results appropriately
- Guidelines:

CONSORT - Consolidated Standards of Reporting (clinical) Trials

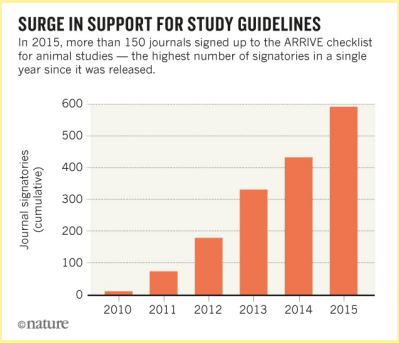
ARRIVE - Animals in Research: Reporting In Vivo Experiments

PPRECISE - Animals in Preclinical Pain Research: Reporting and Methodological Guidelines

NIH - "Rigor and Reproducibility:" Scientific premise, rigor of approach, biological variables, resources and reagents

ARRIVE Checklist
(20 Items)

- Title
  - Accurate
- Abstract
  - Concise key details
- Methods
  - Ethical statement
  - Study design
  - Specific methods/animals
  - Blinding and randomization
  - Statistics
- Results
  - Health and weight
  - Numbers analyzed and excluded
  - Precision and variance
  - Adverse events
- Discussion
  - Interpretation
  - Generalization
  - Funding sources



Nature, 2016

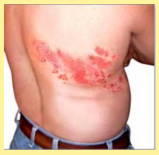
Addressing the Preclinical Challenge

- Models
  - Are the models valid and reliable?
  - How is the pain-related physiology of the mouse/rat similar or distinct from humans?
  - Are commonly occurring comorbidities included?
  - Are the PK/PD properties of the model similar to humans?
- Measures
  - Are the measures valid?
  - Does the response provide and accurate index of a relevant dimension of pain?
  - Is the targeted dimension of pain important to the clinical condition being modeled?

Preclinical Models
(Face Validity)

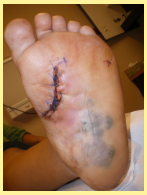
Does the model resemble what we see in the clinic?

Shingles/PHN

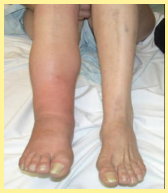


Arthritis

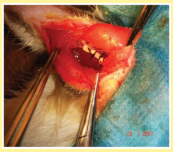
Surgery



CRPS

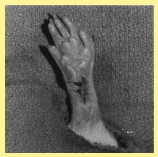


Nerve Injury

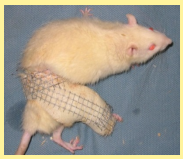


CFA

Incision

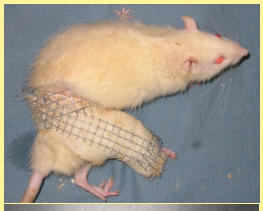


Fracture/Cast



CRPS: The Rodent Fracture-Cast Model

- The most common etiological factors linked to CRPS are distal limb fracture and immobilization.
- Under anesthesia, the distal tibia is fractured and placed in a reinforced cast for 3(mice) to 4(rats) weeks.

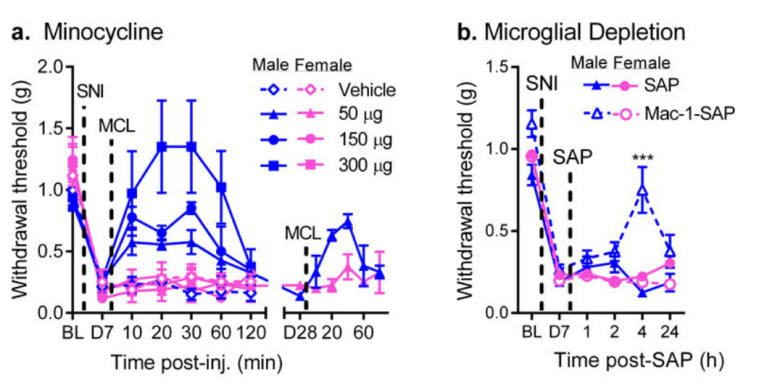


- **Spontaneous extravasation/edema**
- **Warmth**
- **Epidermal thickening**
- **Osteopenea**
- **Allodynia/unweighting**
- **Spontaneous pain**
- **Innate/adaptive immune activation**
- **Anxiety and memory changes**

Preclinical Models
(Influence of Sex)

- Human sex dependence:
  - Disease prevalence
  - Pain severity
  - Comorbidity susceptibility
  - Analgesic responsiveness/side effect profile
- Animal model sex dependence:
  - Degree/duration of nociceptive sensitization
  - Environmental effects
  - Analgesic sensitivity
  - Pathogenic mechanisms
- NIH: Sex (and other biological variables) should be represented in preclinical studies

Preclinical Models
(Influence of Sex)

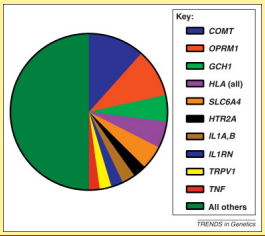


Sorge et al., 2015

Preclinical Models

(Influence of Genetics, Human Observations)

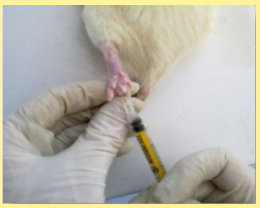
- Twin studies, heritability
  - Pain sensitivity: <10% (mechanical) to >60% (cold pressor)
  - Pain syndromes: 25% IBS, 35% axial spine pain, 50% migraine
  - Analgesic sensitivity: 12% morphine (heat), 60% morphine (cold)
  - Side effects: 30% morphine (RR), 59% morphine (nausea)
- Monogenic (Medelian) pain disorders
  - SCN9A: Activating (more pain), Inactivating (no pain)
  - Hereditary sensory neuropathies (HSNs), Several genes
  - Fam. hemiplegic migraine, CACNA1A, ATP1A2, SCN1A
- Gene association studies
  - COMT, GCH1, MC1R, OPRM1 (pain phenotypes)
  - MDR, CYP2D6 (analgesic responses)

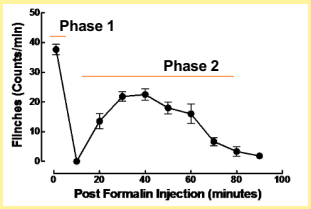


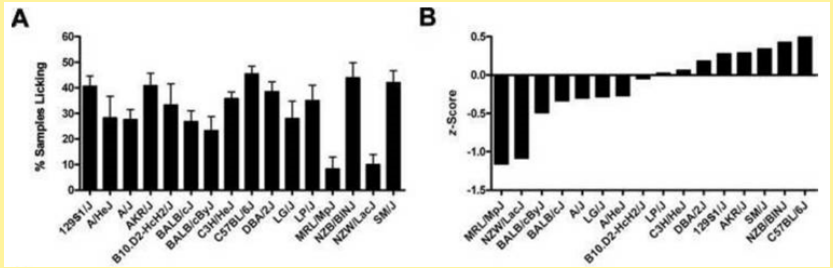
Mogil, Trends in Genetics, 2012

Preclinical Models

(Influence of Genetics)







LaCroix-Fralish et al., 2009

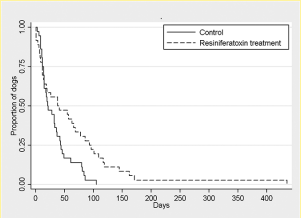
Preclinical Models
(Non-rodent species)

- Rodents offer:
  - Cost/time advantages
  - Genetic opportunities
  - Social acceptability
- Large animals (dogs, horses, primates) offer:
  - Physiology, pharmacology, PK/PD more similar to humans (sometimes)
  - The natural occurrence of similar diseases, e.g. **OA**, cancer, neuropathy, etc.
  - Some functions more easily studied, e.g. gait
  - Ability to work with complex behaviors/cognitive tasks
  - Better size for some testing, e.g. structural/functional imaging
- Available models
  - Acute nociception (dogs, primates)
  - Algogen injection (primates)
  - UV sensitization (pigs)
  - OA, ACL injury (dogs)
  - L6, L9 primate nerve ligation model (primates)

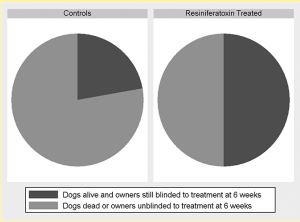
RTX Testing in Canine Cancer Patients

- Patients – 72 Companion dogs with bone cancer pain.
- Treatments – Standard analgesics versus analgesics plus 1.2ug/kg i.t. RTX.
- Dogs failing treatment were then unblinded.

Improved pain survival



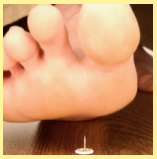
6wk Efficacy



Brown et al., Pain, 2015

Preclinical Measures
(Reflexive Testing)

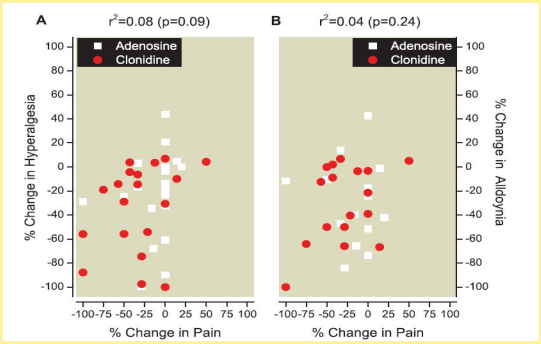
- "Reflexive" or "evoked" testing
  - Mechanical, e.g. von Frey filaments
  - Thermal, e.g. thermal plantar
  - Very quick, straightforward, objective
  - Inexpensive




- Problems?
  - Nociceptive fiber types activated
  - Generally skin tissue targeted
  - Poorly correlated with operant responses
  - Clinical complaint: "My pain is almost always there and it limits what I do, my ability to think, being with my family, my sleep and makes me feel depressed."

Analgesia vs. Anti-hyperalgesia

- Twenty-two subjects with CRPS
- Allodynia and hyperalgesia assessed
- Clonidine 100ug or adenosine 2mg intrathecal

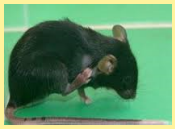


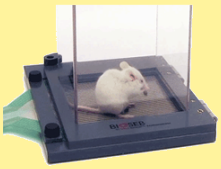
Rauck et al. Pain. 2015

Preclinical Measures
(Spontaneous/Ongoing Pain)

"Body Language"

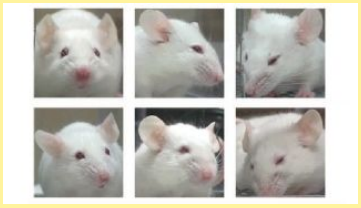
Flinching, guarding





Postural changes/weight bearing

Face analysis

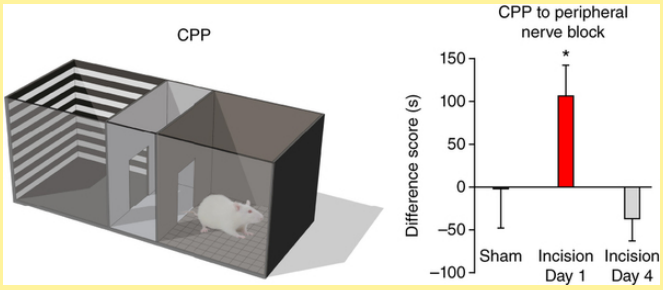


Ultrasonic vocalizations

Langford et al., 2010

Preclinical Measures
(Spontaneous/Ongoing Testing)

- Conditioned Place Preference

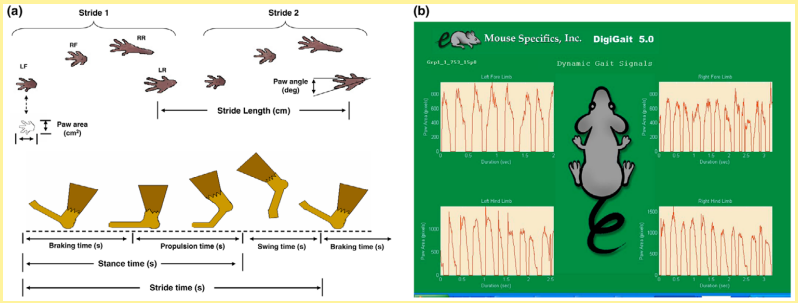


Navratilova and Porreca, 2014

- Other "operant" assays:
  - Reward-conflict – receiving a reward with corresponding aversive stimulus
  - Avoidance-escape – forced selection between alternative aversive stimuli (one nociceptive)

Preclinical Measures
(Functional Testing)

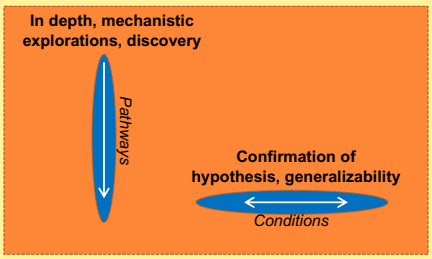
- Gait analysis:
  - Incision, Osteo and Rheumatoid arthritis, Multiple sclerosis, CRPS, Chemotherapy-induced pain, Neuropathic pain
  - Analgesics reversed gait abnormalities in some but not all models, e.g. SNI, incision.



Vincelette et al., 2007

Preclinical Models
(Breadth of Experimental Factors)

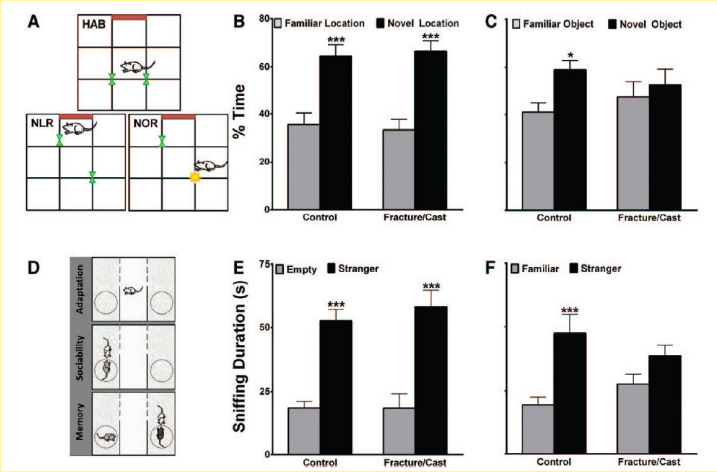
- For *discovery*
  - Stringently standardize experimental conditions.
  - Use multiple rigorous, complementary approaches focused on a clear hypothesis, e.g. pharmacological, genetic, biochemical, electrophysiological, optogenetic, etc.
- For *translation* we may specifically examine the impact of:
  - Sex
  - Genetics, species
  - Age
  - Physiological comorbidities
  - "Psychological" comorbidities
  - PK/PD



Pain – So what's the problem?

- It's common
  - Chronic pain - ~25% of the population, >50% of veterans, overall prevalence is increasing as is disability
  - Acute pain - Moderate-severe in ~30% postoperatively
  - Cancer pain - >50% all stages, >30% after cure
- It's costly
  - Chronic pain - $600B annually in the US, and costs are increasing faster than overall healthcare
  - Acute pain - Discharge, readmission, recovery, complications
  - Cancer pain - Direct + Indirect ~$900/mo
- It's difficult to treat
  - Drug Trials - <50% of participants receive >50% pain relief
  - Multiple treatments and multimodal treatment is common
  - Functional improvements difficult to demonstrate
- Opioid crisis

Preclinical Measures
(Memory and Social Interactions)



Tajerian et al., 2015

Translational Studies
(Outcome Domains)

IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

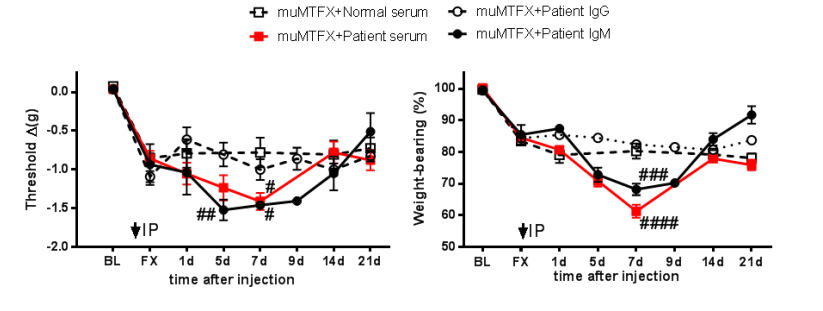
- Pain
  - Patient report, analgesic use
- Physical function
  - Interference scales
- Emotional function
  - Depression, anxiety
- Pt. impression of change
  - PGIC scale
- Symptoms/adv. events
  - Active/passive capture
- Participants , reporting
  - CONSORT

IMMPAAS: Initiative on Methods, Measurement, and Pain Assessment in Animal Studies

- Pain
  - Evoked, spontaneous, operant
- Physical function
  - Activity, gait, running
- Emotional/cognitive function
  - Depression, anxiety, memory
- Side effects, PK/PD, toxicity
  - Sedation, balance, organ tox.
- Subjects, reporting
  - ARRIVE

Example: Autoimmunity Translation

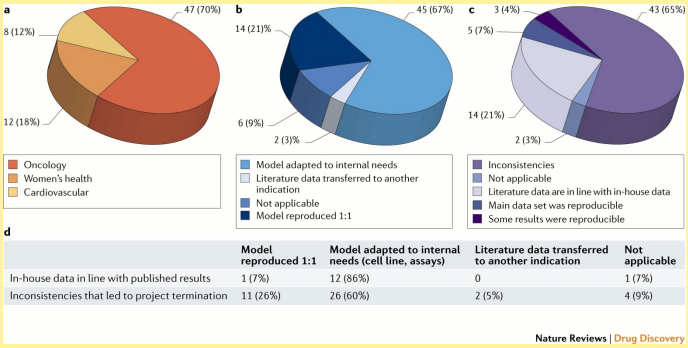
- Autoimmunity in CRPS
  - Anti-mACh, beta-2, alpha-1, anti-nuclear antibodies
  - Some patients treated with IVIG



The Reproducibility of Preclinical Testing

"At least 50% of published studies, even those in top-tier academic journals, can't be repeated with the same conclusions by an industrial lab."

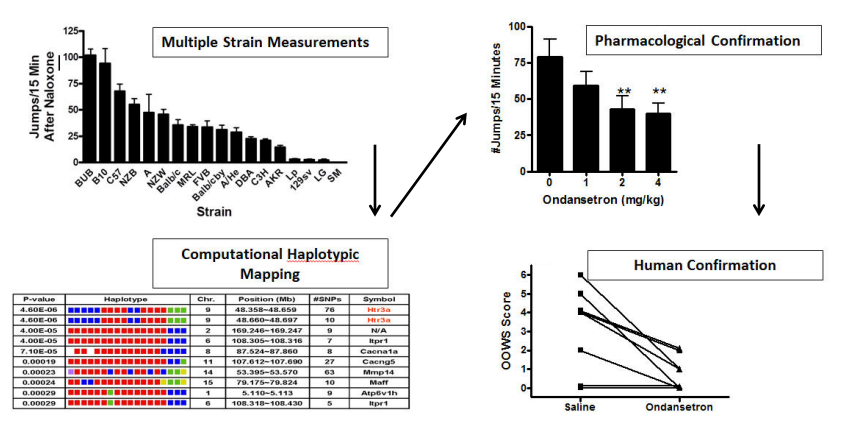
Bruce Booth, venture capitalist, 2011



Bayer Healthcare, 67 laboratory projects

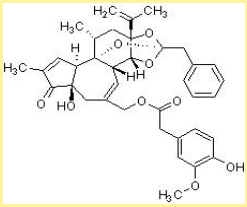
Preclinical Models

(Influence of Genetics)



Chu et al., 2009

Intrathecal Resiniferatoxin (RTX)



- RTX is a potent, cytotoxic TRPV1 agonist.
- TRPV1 is predominantly expressed on unmyelinated nociceptive neurons.
- Intrathecal and local administration of RTX desensitizes and ablates nociceptive terminals.
- Touch, proprioception and motor control are not altered by RTX administration.
- General anesthesia is required for administration.
- Pilot studies showed dogs with cancer-related bone pain improve after i.t. RTX injection.

What approaches were used in trials?
(A very short List)

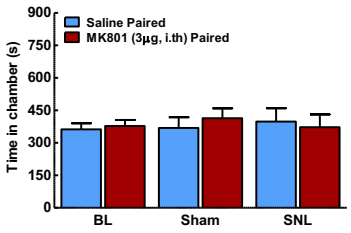
- CCR2 antagonists
  - Posttraumatic neuralgia
- TRPV1 antagonists
  - AMG 517 (others), Hyperthermia
  - OA, Dental pain, GERD
- FAAH1 antagonists
  - OA
- NK1 antagonists
  - Postoperative pain
  - PDN
- "Glial inhibitors" (Minocycline, Propentofylline)
  - Persistent pain after discectomy, Hand surgery, Radiculopathy
  - PHN
- NMDA/AMPA antagonists
- P2X antagonists

10.7% of analgesics entering Phase 1 trials are eventually approved*

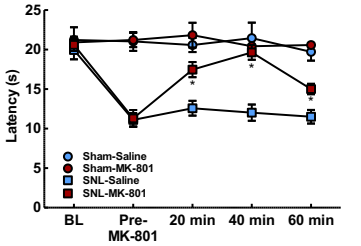
Hay et al., Nat. Biotech., 2014

Blockade of hypersensitivity is not the same as blocking ongoing pain

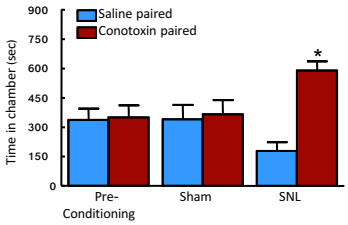
Spinal MK-801 does not induce CPP



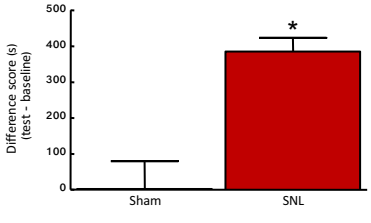
At a dose that fully reverses thermal hypersensitivity



Spinal ω-conotoxin induces CPP



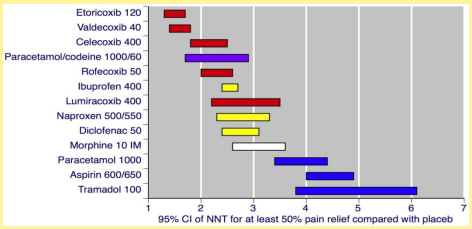
Spinal ω-conotoxin paired chamber



Courtesy Dr. Frank Porreca

Numbers Needed to Treat/Harm (NNT/NNH)

Acute Pain, 50% Relief



Oxford League Table, 2007

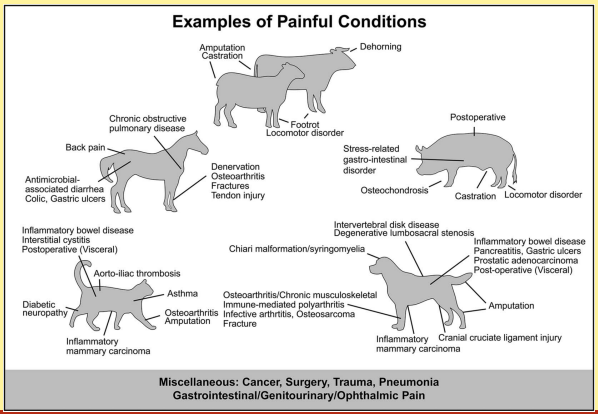
Chronic Pain, 50% Relief

Drug	Condition	NNT 50% relief	NNH
Opioids [1,2]	Neuropathic pain	2.5[12]- 4.3 [12]	4.2 -8.3
Tramadol [3,4]	Neuropathic pain Post-surgical	3.4[3] - 4.7 [12] 2.4 – 4.8 [4]	8.3
TCAs: Amitryptyline[5] Nortryptyline	Neuropathic pain	3.6 [5,12]	6 (minor) - 28 (major)
Gabanoids Gabapentin [6,7] Pregabalin [8,9]	Neuropathic pain Central Neuropathic Diabetic neuropathy PostHerpeticNeuralgia Fibromyalgia	7.2 – 7.7 [12] 5 [8] 2.9 - 5 [6,8] 3.9 [8] 13-22 [9]	3.7 (minor)
SNRIs: Venlafaxine[5] Duloxetine[10]	Neuropathic pain	3.1[5] 6 – 8 [10]	16.2 (major) 9.6 (minor)
Paracetamol[11]	Chronic arthritis	4-5[11]	12 (GI SEs)
Lignocaine patch[12] Capsaicin patch[13]	Peripheral Neuropathic Pain	4.4[12]. 10.6[13]	Minimal

Gov't. of Western Australia Dept. of Health

"Natural" Animal Pain Models

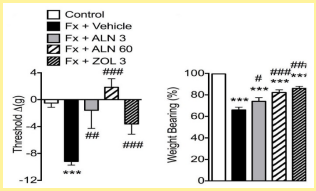
- Advantages:
  - Diverse genetics, both sexes, all ages, different environments, etc.
  - Evoked QST responses, spontaneous behaviors, social interactions, activity levels, other measures

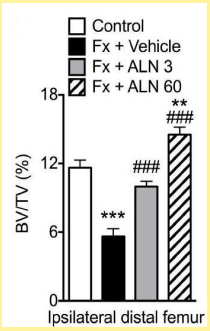


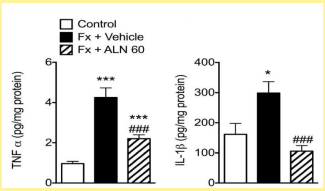
Klinck et al., Pain, 2017

Example: Bisphosphonate Translation

- **Clinical data:** Several small controlled trials – alendronate, clodronate, pamidronate and neridronate
- **Zoledronate?** – Animal data used for successful Orphan/Fast Track FDA status







- **Ahmad and Kumar, 2015:** Monthly zoledronate reduces pain in CRPS I after electrical burn