IMMPACT-XIX

Accelerating The Development Of Precision Pain Medicine

Preclinical research obstacles and opportunities in developing precision pain medicine: An overview

Andrew SC Rice MB BS, MD, FRCP, FRCA

Imperial College London

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

To illustrate arguments will focus on:

- Neuropathic pain
- Animal models

…..although the issues and concepts are generic

- **External Validity:**
  - The disease models
  - Profiling
  - Outcome measures

- **Internal validity:**
  - Susceptibility to bias in design, conduct, analysis and reporting of pre-clinical data

Lancet Neurol 2015; 162–73

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Nanna B Finnerup*, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace

Efficacy outcomes generally represent only modest gains

- **Recommendation:**
  - **Strong** recommendation for as **first-line** treatment:
    - Tricyclic antidepressants (mainly amitriptyline)
    - SRNI (mainly duloxetine)
    - Pregabalin & gabapentin
  - **Weak** recommendation for as **second-line**:
    - Lidocaine 5%
    - Capsaicin 8%
    - Tramadol
  - **Weak** recommendation for as **third-line**:
    - Strong opioids
    - Botulinum toxin A

	$NNT_{50\%}$ (95% CI)
TCA	3.6 (3.0 – 4.4)
SNRI (mainly duloxetine)	6.4 (5.2 – 8.4)
Pregabalin	7·7 (6·5 – 9·4)
Gabapentin (inc ER and enacarbil)	7·2 (5·9 – 9·21)
Lidocaine 5%	n.d
Capsaicin 8%	10·6 (7·4 – 19·0)
Tramadol	4.7 (3.6 – 6.7)
Strong opioids	4.3 (3.4 – 5.8)
Botulinum toxin	Uncertain

Finnerup et al Lancet Neurology 2015;14:162

Key Features of Neuropathic Pain

Pain caused by a lesion or disease affecting the somatosensory system

- Pain occasionally generated in response to damage to sensory nervous system
- Pain in absence of a noxious stimulus:
  - Spontaneous continuous
  - Spontaneous paroxysmal (lancinating)
  - Evoked (stimulus dependant) pain

Variably associated with sensory perturbations:

- **Sensory Loss:**
  - Pain in areas of sensory loss - *Anaesthesia Dolorosa*
- **Sensory Gain:**
  - *Allodynia* – pain in response to an innocuous stimulus
  - *Hyperalgesia* – increased response to a painful stimulus

THE MODEL:

Reproducing the Disease/Lesion

Pain, 6 (1979) 175—182

THE PRODUCTION AND PREVENTION OF EXPERIMENTAL ANESTHESIA DOLOROSA

P.D. WALL, J.W. SCADDING and M.M. TOMKIEWICZ

Cerebral Functions Group, Department of Anatomy, University College, Gower Street London WC1E 6BT (Great Britain)

Pain, 7 (1979) 103—113

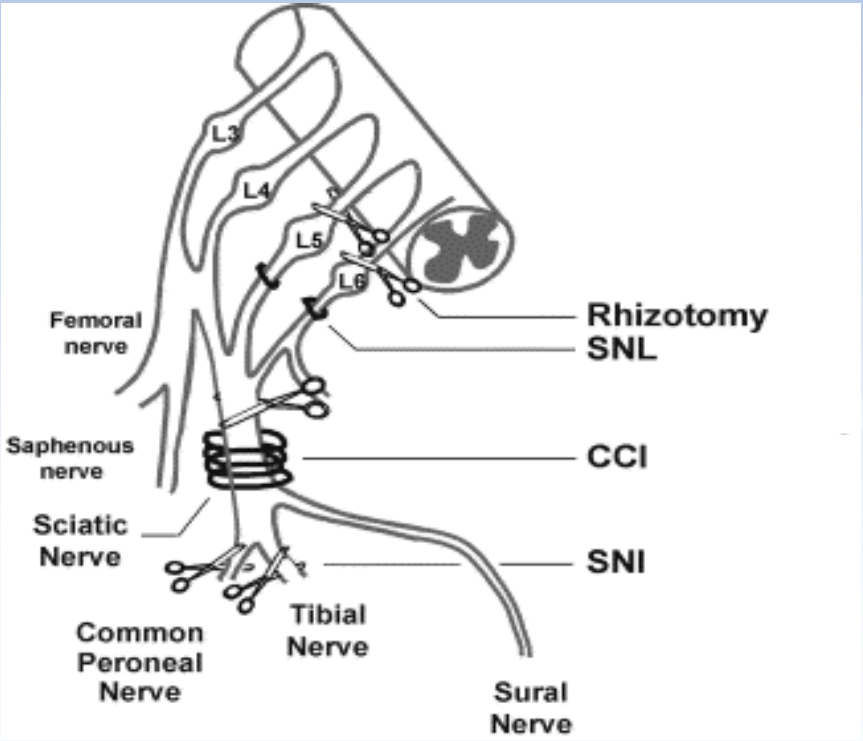
Research Reports

AUTOTOMY FOLLOWING PERIPHERAL NERVE LESIONS: EXPERIMENTAL ANAESTHESIA DOLOROSA

P.D. WALL *, M. DEVOR, R. INBAL, J.W. SCADDING, D. SCHONFELD, Z. SELTZER and M.M. TOMKIEWICZ

Neurobiology Unit, Institute of Life Sciences, Hebrew University, Jerusalem (Israel) and Cerebral Functions Group, Department of Anatomy, University College, London WC1E 6BT (England)

Animal Models of Traumatic Nerve Injury



Heterogeneous Pathologies Associated with Neuropathic Pain

- Trauma
- Ischaemia
- Infection/Inflammation
- Cancer
- Chemical injury, including drugs
- Metabolic and endocrine neuropathies
- Compression
- Genetic channelopathies
- Idiopathic

Neuropathic Pain:
Systematic Review & Meta-Analysis of 4796 Animal Model Publications

Currie, Sena, Wodarski, Morland et al

Neuropathic pain model	Number of publications from screening
Chronic Constriction Injury	1402
Spinal Nerve Ligation	916
Diabetes-induced	678
Partial Sciatic Nerve Ligation	396
Spinal Cord Injury	384
Chemotherapy-induced	341
Spared Nerve Injury	228
Crush Sciatic Nerve	78
Trigeminal Nerve Ligation	70
Transection Of The Spinal Nerve	54
Nerve Root Ligation	46
Transection Of The Sciatic Nerve	38
Herpes Zoster-induced	35
Alcohol-induced	36
Anti-retroviral Drug-induced	26
HIV Gp120-induced	27
CCI Of Infraorbital Nerve	21
Root Transection	20

Protocol Registered at:

www.dcn.ed.ac.uk/camarades/research.html#protocols

CAMARADES

imi EuroPain

NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

The University of Edinburgh

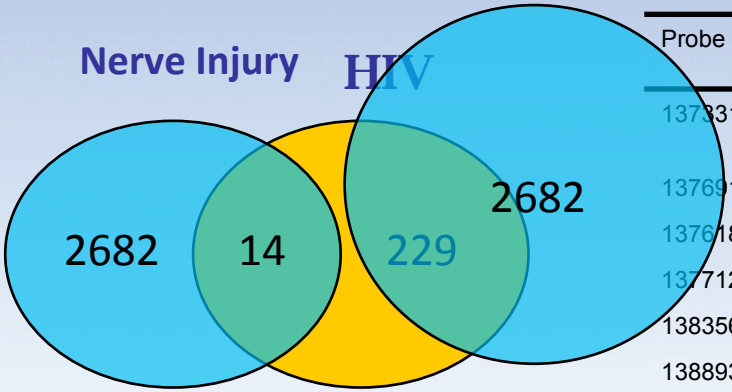
Imperial College London

Heterogeneity of Neuropathy Models

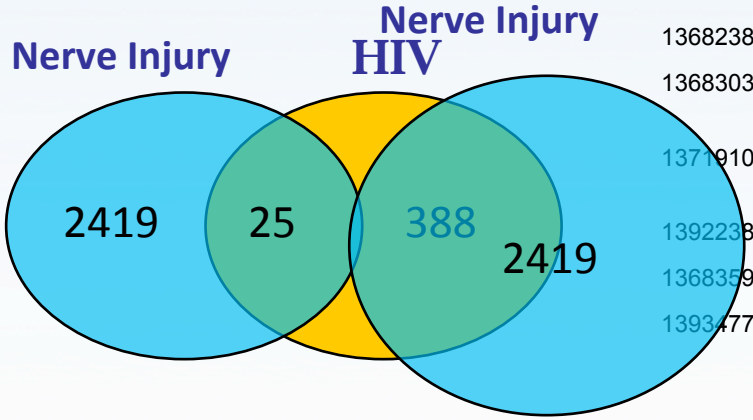
Comparison of Gene Expression in Traumatic and HIV Neuropathies

(Maratou et al Eur J Pain 2009;13:387-398)

Upregulated



Downregulated



Probe Set ID	Gene Symbol	SNT	gp120+ddc
1373315_at	Arnt2	1.4	1.3
1376911_at	Atp2B4_predicted	2.9	1.3
1376182_at	Bptf_predicted	1.8	1.2
1377121_at	Dlg5_predicted	1.5	1.2
1383564_at	Irf7	3.4	1.2
1388932_at	Lama5	1.8	1.3
1377103_at	Midn_predicted	1.6	1.3
1387154_at	Npy	8.6	1.9
1368238_at	Pap/Reg2	22.3	1.2
1368303_at	Per2	2.6	1.3
1371910_at	Scube1_predicted	1.6	1.4
1392238_at	Slc4a8_predicted	2.2	1.3
1368359_a_at	Vgf	3.5	1.3
1393477_at	---	5.0	1.5

Commonly Upregulated

- Bayes moderated t p< 0.05
- >1.2-fold difference
- 10% FDR
- Affymetrix Gene Chip Rat Genome 230 2.0

Disparity of Biochemical Responses of Dorsal Root Ganglion Cells in Models of Peripheral Nerve Trauma and Drug-Induced Neuropathy

Boateng et al Eur J Pain 2015;19:236

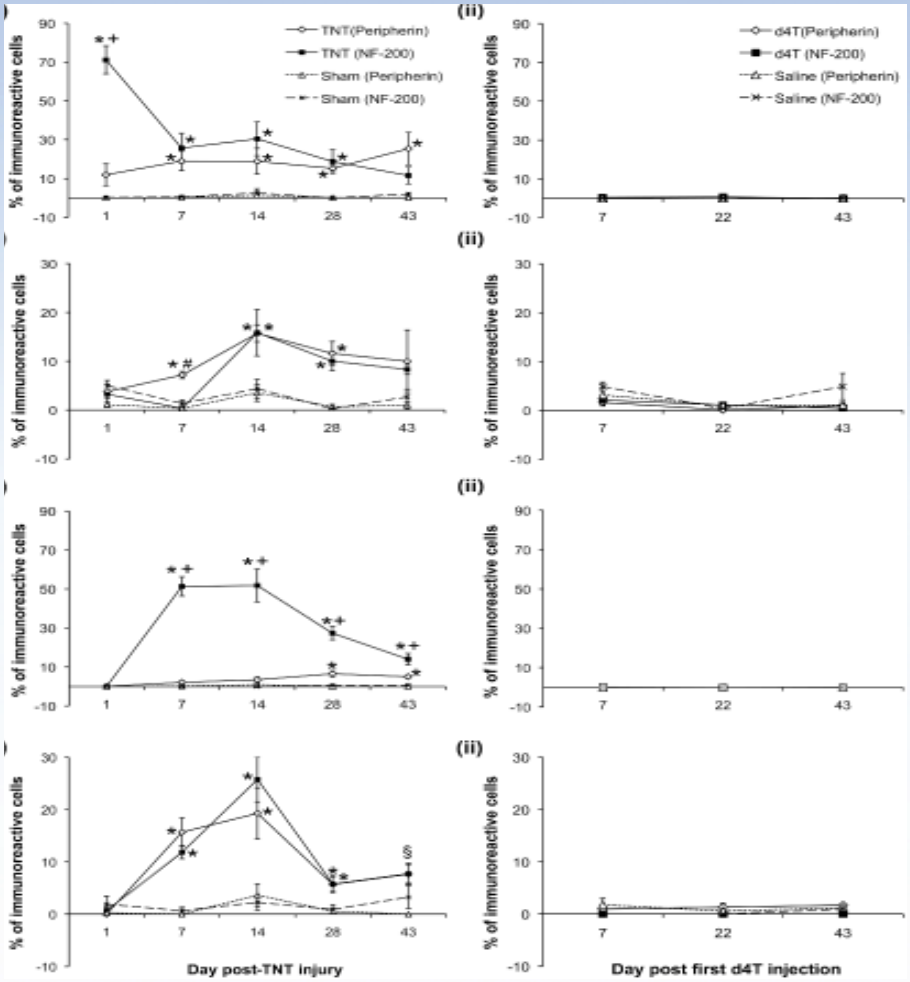
Nerve Trauma | **Drug-Induced Neuropathy**

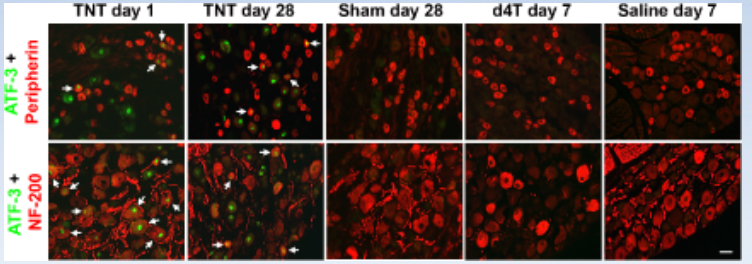
ATF3

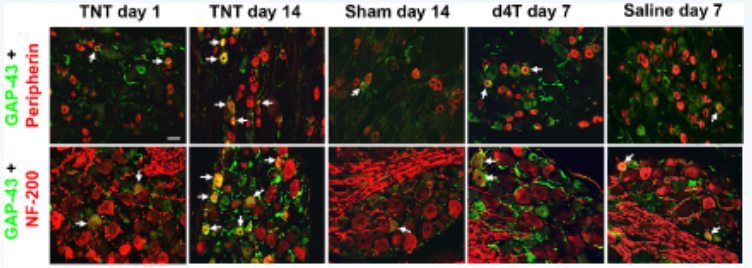
GAP-43

NPY

Galanin

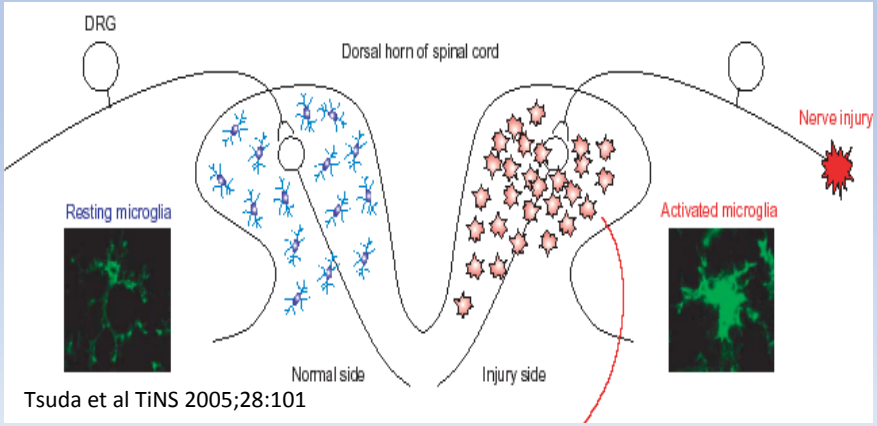




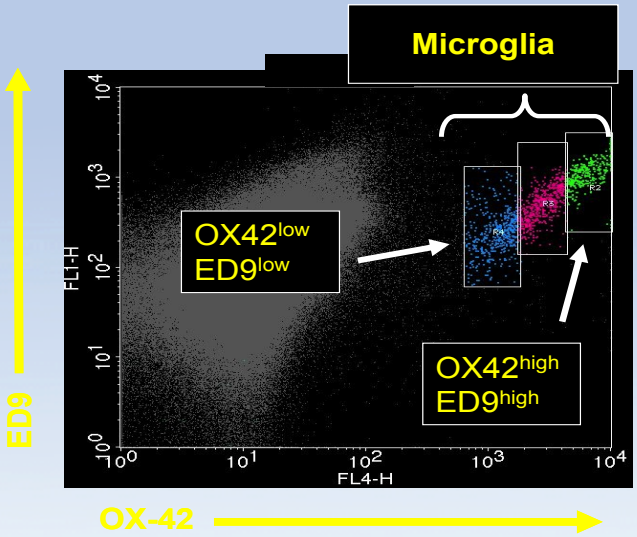


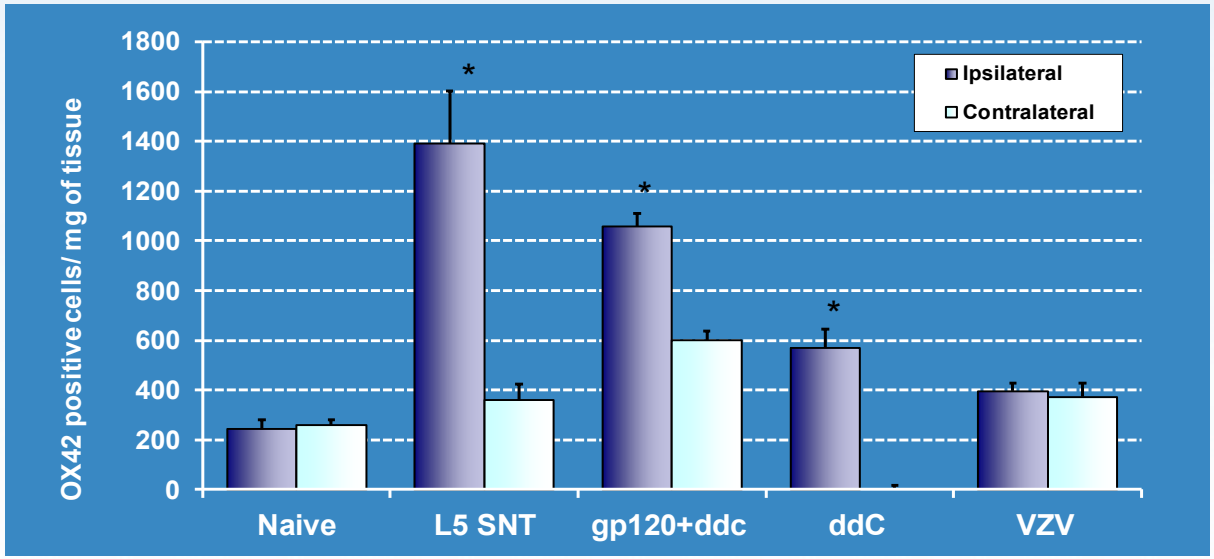
Heterogeneity of Spinal Microgliosis in Rat Neuropathy Models

(Blackbeard et al Eur. J Pain 2012;16:1357 & Blackbeard et al J. Neurosci. Meth. 2007;164:207)



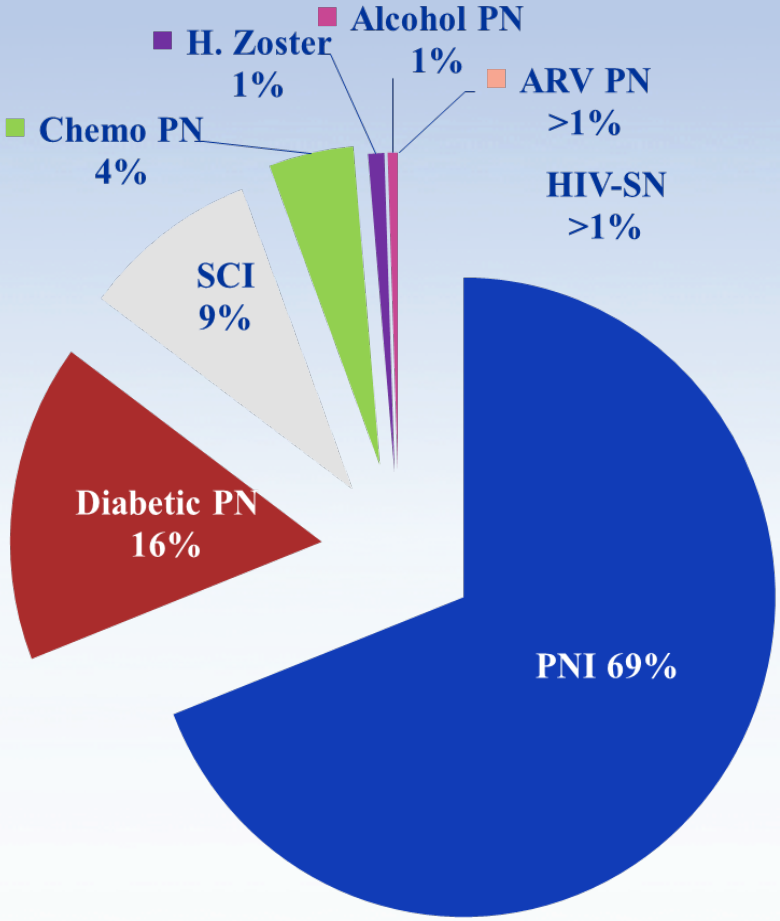
Tsuda et al TiNS 2005;28:101





4236 Animal Model Reports

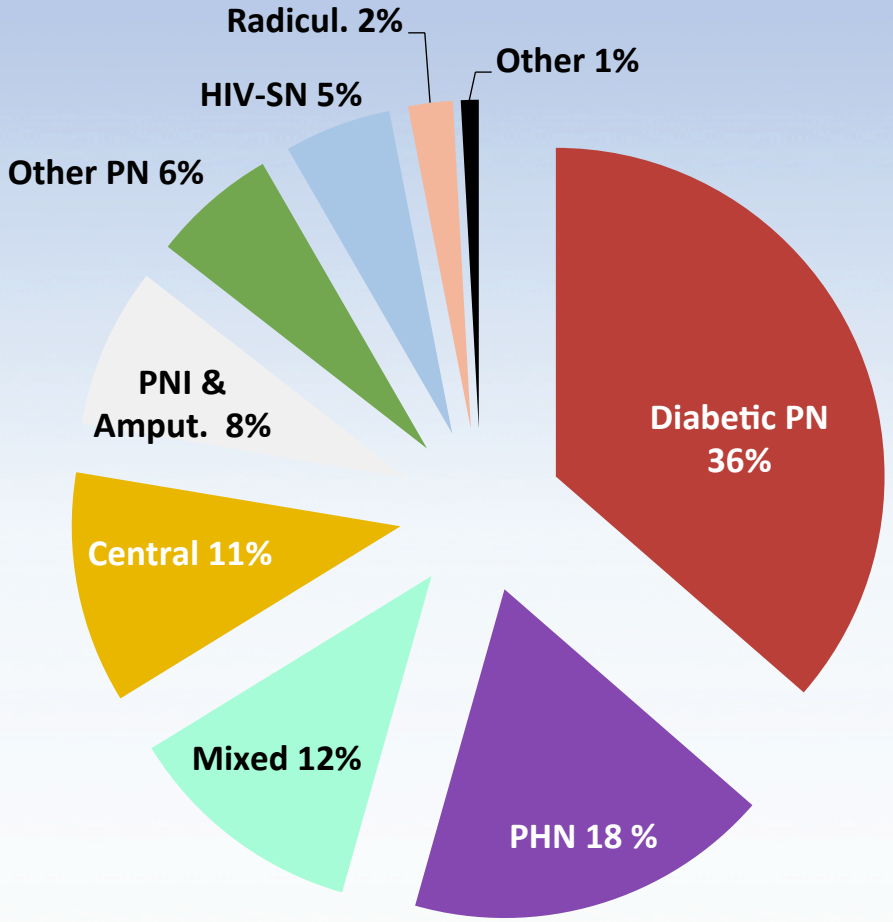
Currie, Sena, Wodarski, Morland et al



229 RCTs

Finnerup et al

Lancet Neurology 2015;14:162



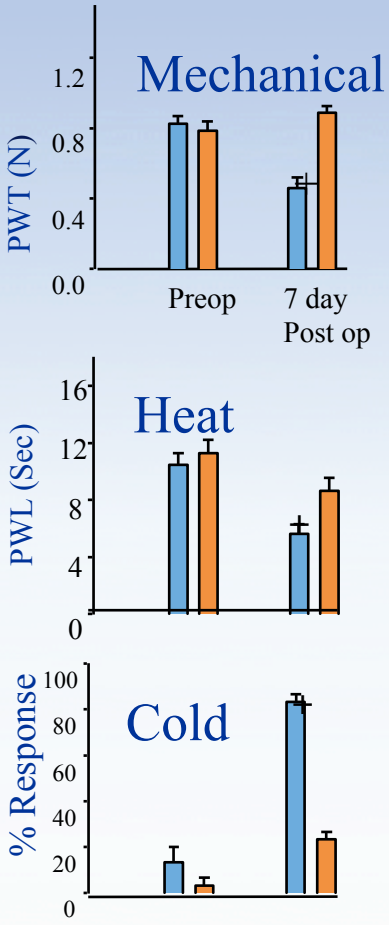
Challenge 1:

To develop and systematically profile a portfolio of animal models that accurately reflect the range, clinical presentations and pathological heterogeneity of diseases associated with neuropathic pain

Profiling Measures

Outcome Measures

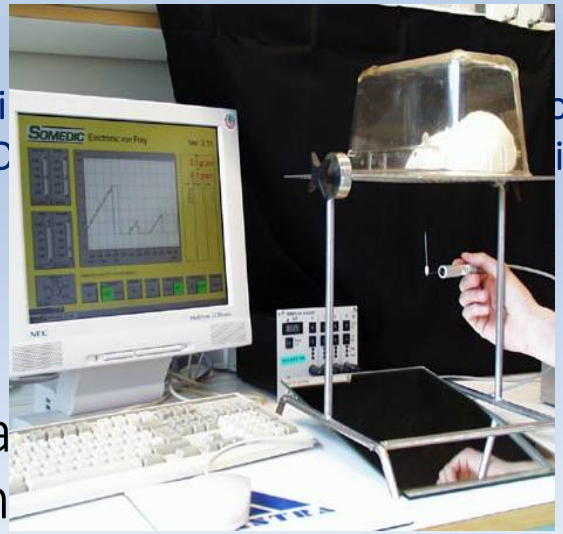
Limb Withdrawal to Sensory Stimuli



Bridges et al Br. J. Pharmacol. 2001:133:586

Left-L5 spinal nerve transected
Right- sham control

Domai ons for
Core C in RCTs

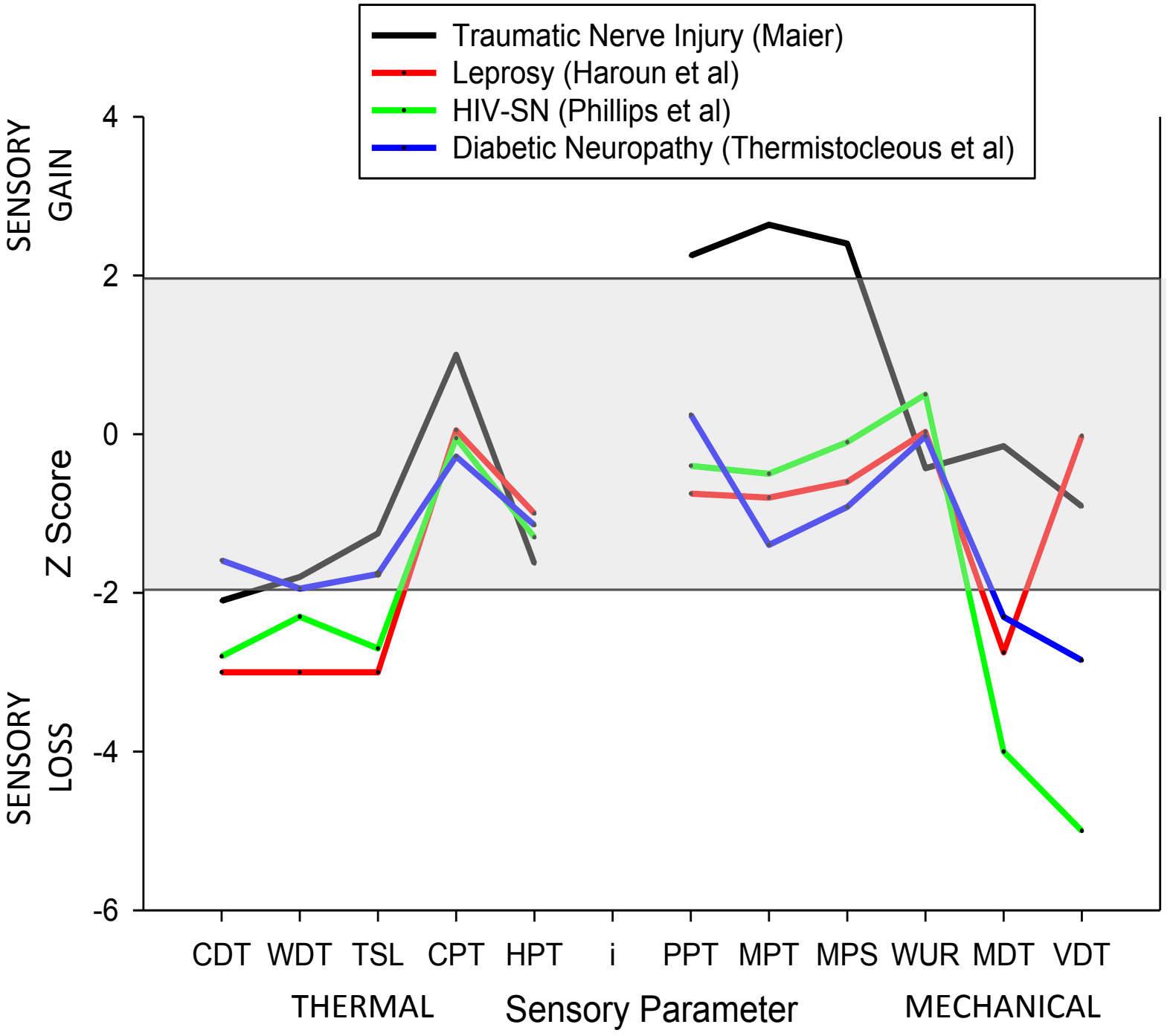


- Pa
  ch
  - Spontaneous continuous
  - Spontaneous paroxysmal

Portfolio of Neuropathic Pain Outcomes

	Animal Studies	Human RCTs
Evoked hypersensitivity	+	+/- ***(for baseline QST phenotyping)***
Spontaneous continuous pain	–	+ ***(Usual 1º efficacy measure)***
Spontaneous paroxysmal pain	–	+/-
Co-morbidity **•Physical function** **•Emotional function** **•Circadian rhythm disturbance**	–	+
Adverse events	–	+
Global impression	–	+

Evoked sensory signs as profiling rather than as outcome measure?


Traumatic Nerve Injury (Maier)
Leprosy (Haroun et al)
HIV-SN (Phillips et al)
Diabetic Neuropathy (Thermistocleous et al)
SENSORY GAIN
SENSORY LOSS
Z Score
4
2
0
-2
-4
-6
CDT
WDT
TSL
CPT
HPT
i
PPT
MPT
MPS
WUR
MDT
VDT
THERMAL
Sensory Parameter
MECHANICAL

PAIN® 155 (2014) 2263–2273

PAIN®

www.elsevier.com/locate/pain

The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study

Dyveke T. Demant [a], Karen Lund [b], Jan Vollert [c], Christoph Maier [c], Märtha Segerdahl [d,e], Nanna B. Finnerup [b], Troels S. Jensen [b], Søren H. Sindrup [a,*]

PAIN® 153 (2012) 1193–1198

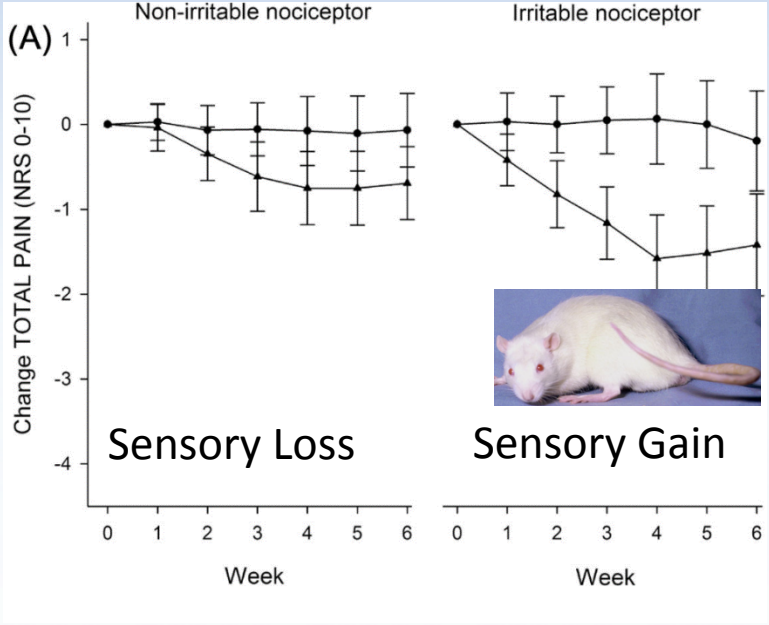
PAIN®

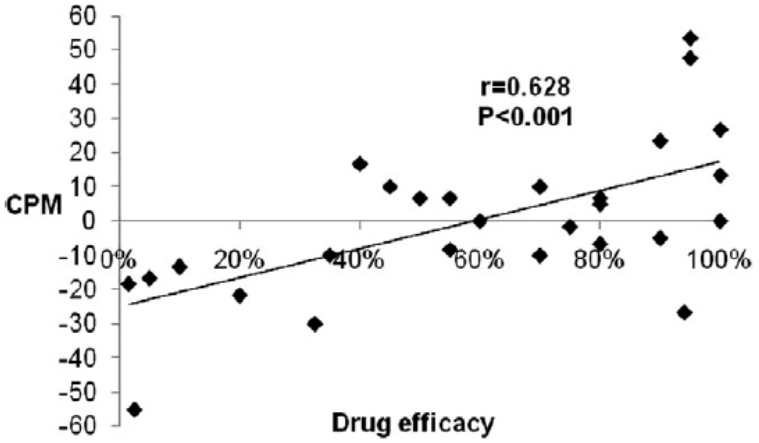
www.elsevier.com/locate/pain

Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy

David Yarnitsky [a,b,*], Michal Granot [c], Hadas Nahman-Averbuch [b], Mogher Khamaisi [d], Yelena Granovsky [a,b]

[a] Department of Neurology, Rambam Health Care Campus, Haifa, Israel





Challenge 2:

To develop profiling tools for use in animal models which are aligned with clinical profiling biomarkers which have predictive utility in pain clinical practice/trials eg

a. Quantitative sensory profiles
b. DNIC / Conditioned pain modulation

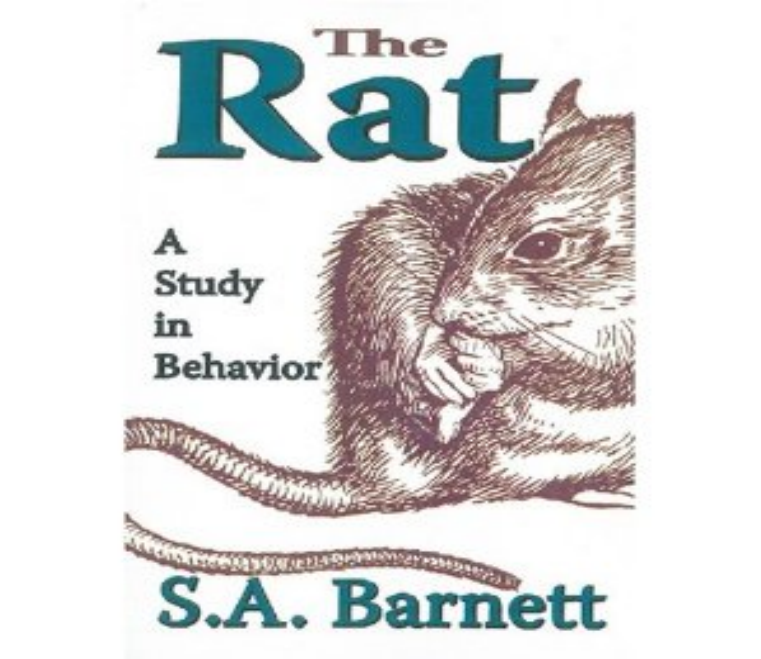
OUTCOME MEASURES

Outcome Measures:

Reproducing the Clinical Signs Associated with Neuropathic Pain *(Not Symptoms!)*

- Presence/absence of pain cannot be directly measured in humans or animals
- Measurement of pain in patients reliant on “patient reported outcomes”
- Pain can only be inferred in animals by measuring changes in **ethologically relevant** behaviours characterised by appropriate pharmacological perturbations

Ethologically Relevant Outcome Measures



biology
letters
Animal behaviour

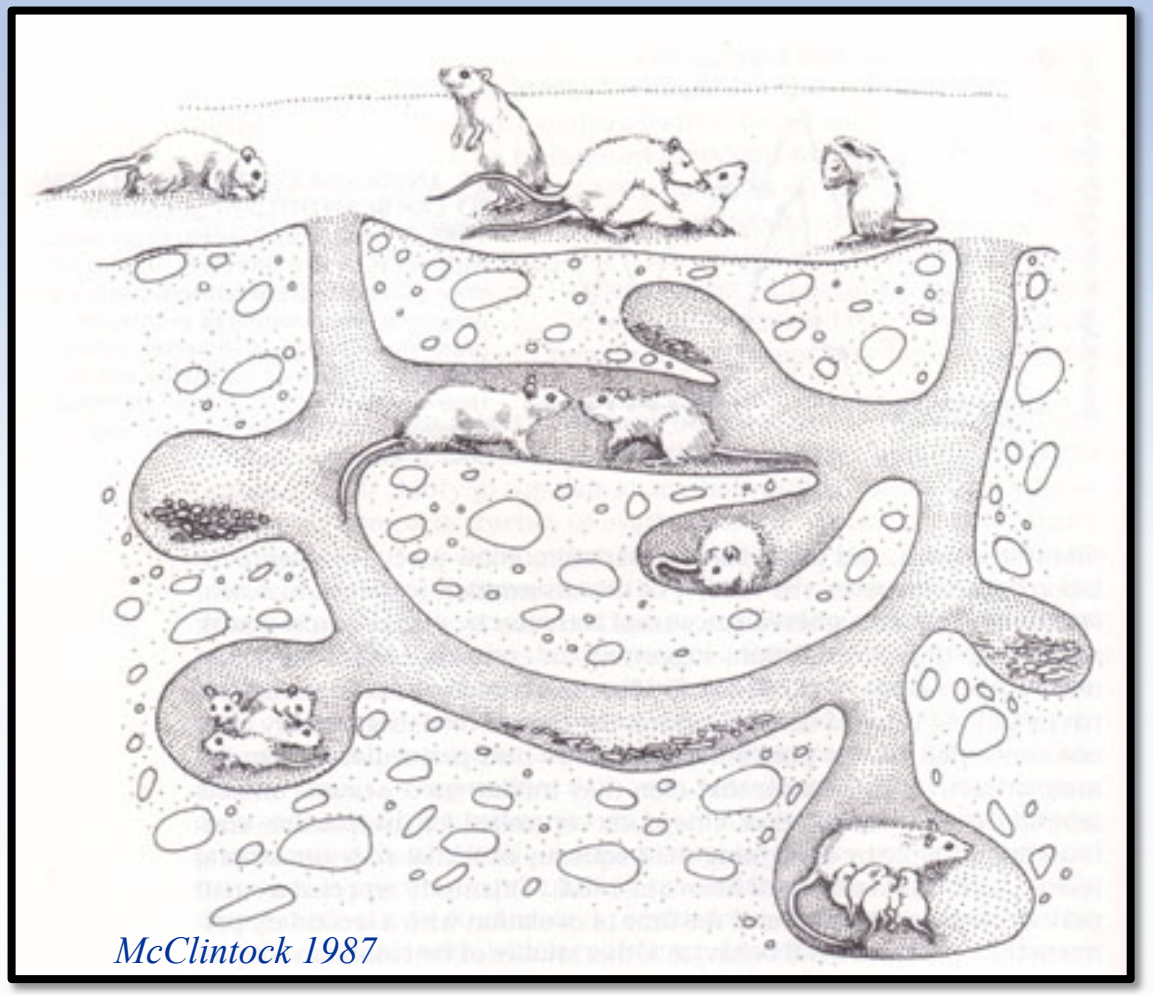
Biol. Lett.
doi:10.1098/rsbl.2012.0554
Published online

Opinion piece

Pro-sociality without empathy

Marco Vasconcelos[1,2], Karen Hollis[3,4], Elise Nowbahari[4] and Alex Kacelnik[2,*]

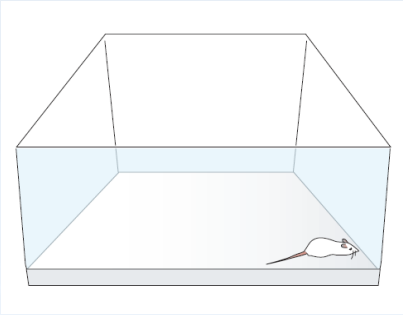
Norway Rat "Breeding Deme"



THIGMOTAXIS IN OPEN FIELD

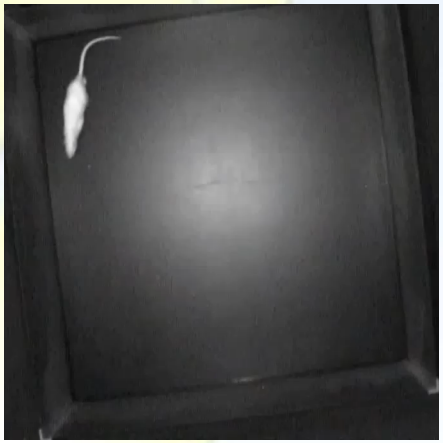
Hasnie et al Neuroscience 2007;144:1495

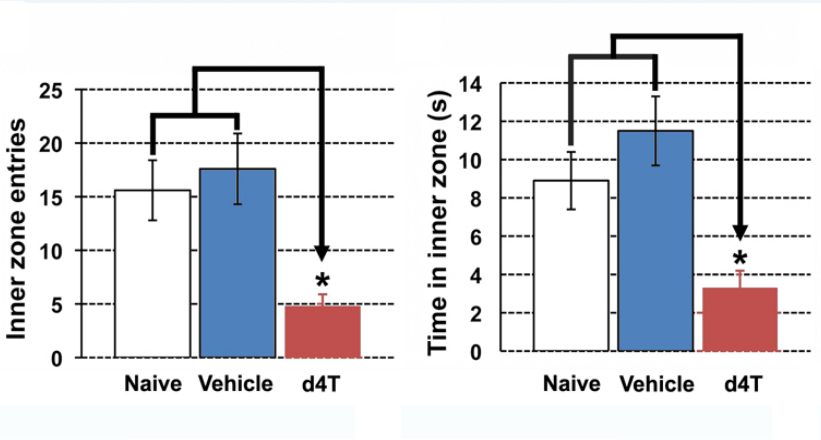
- Construct: Behavioural conflict - limiting exposure (to risk of predation) vs exploratory drive
- Apparatus: Open field arena

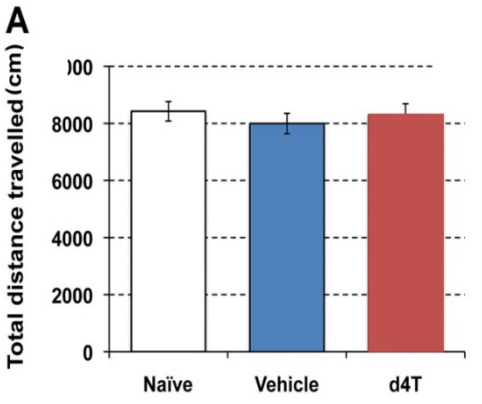


Naive

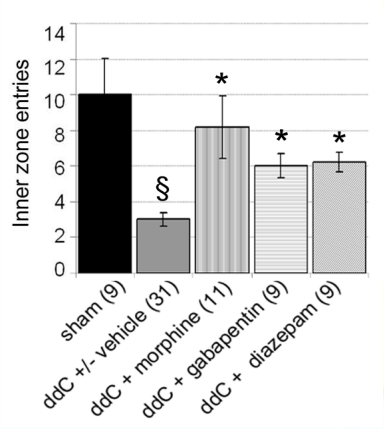
Stavudine (d4T)-induced Neuropathy







Huang et al Pain 2013;154:560



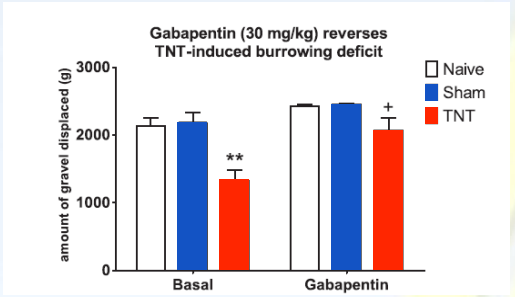
Gabapentin 30 mg/kg, i.p.
Morphine 2.5 mg/kg, i.p.
Diazepam 1 mg/kg, i.p.

Wallace et al Neurosci. Lett 2008;448:153-156

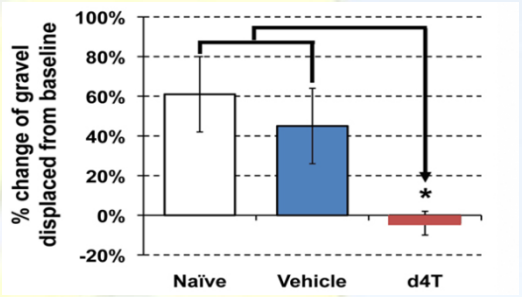
BURROWING

- Construct: Pharmacologically-sensitive perturbation of ethological burrow maintenance behavioural by fossorial rodents
- Apparatus: Substrate-filled tube

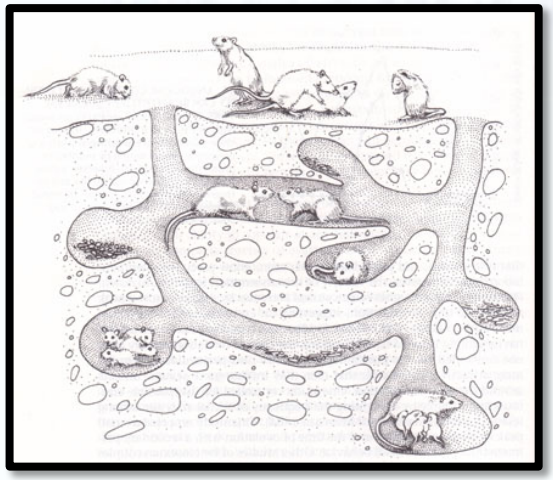
Deacon Nat Protocols. 2006;1:118
Andrews et al Eur J Pain 2012;16:485
Huang et al Pain 2013;154:560;
Rutten et al. Eur J Pain 2014;18:204

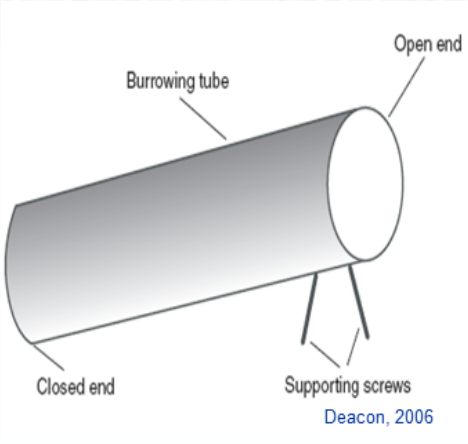


Andrews et al Eur J Pain 2012;16:485



Huang et al Pain 2013;154:560;

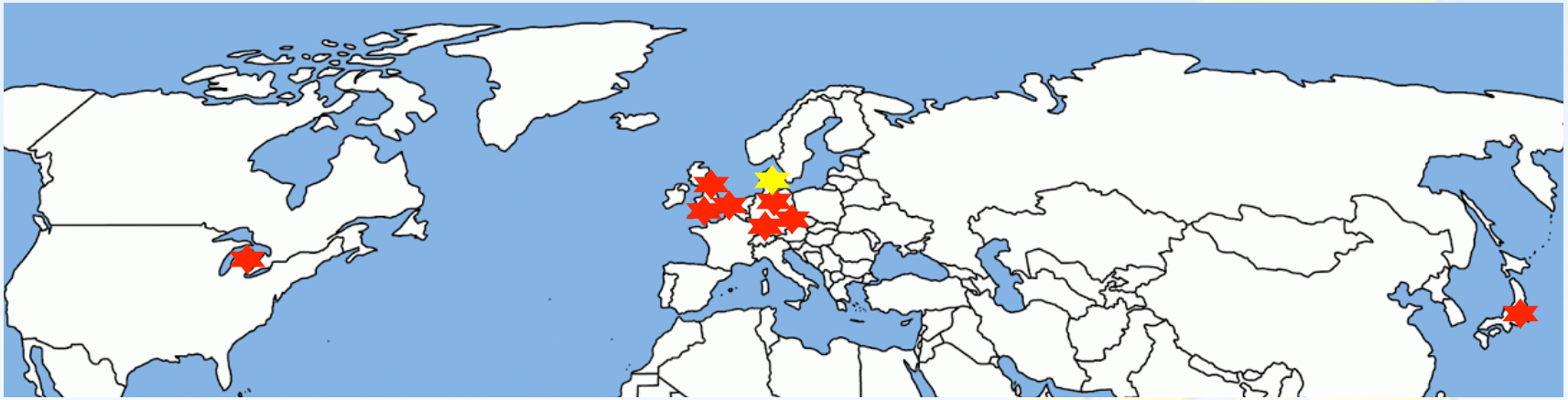




Deacon J.Vis.Exp. 2012;59:e2607

Prospective Multicentre Replication of Burrowing as Outcome Measure

Model: Intra-Plantar Complete Freund' Adjuvant in Rats



Lilly

Imperial College (Rice)
Manchester Univ (Gardiner)
Lilly

Asahi Kasei

Lundbeck (statistics)

Grunenthal
Boehringer-Ingelheim
Heidelberg Univ (Treede)

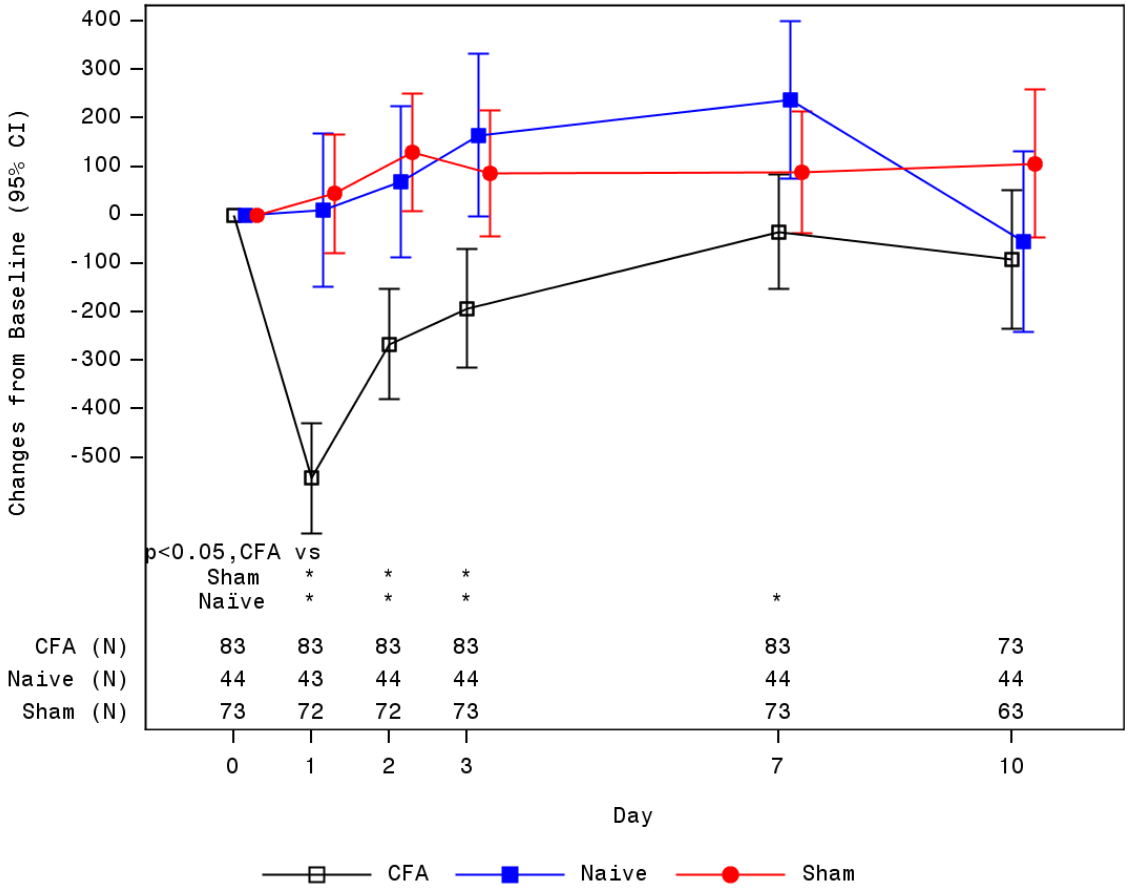
imi Europain

Wodarski et al PAIN in press

Primary Outcome - Cross Centre Validation

Wodarski et al PAIN in press

Intraplantar CFA in Rats: Mean Change from Baseline in Amount Burrowed (g) per Timepoint (PPS, MMRM)



Model: change from baseline in burrowing explained by group, time, and group-by-time and baseline burrowing-by-time interactions

Appropriate Pharmacology

- Complex behaviours influence by multiple “illness related” factors, including, but not specifically, pain
- Relevance of a behaviour to pain needs to be a validated by appropriate responses to drugs which do/do not have efficacy in the matched clinical condition.

EJP
European Journal of Pain

ORIGINAL ARTICLE

Pharmacological validation of a refined burrowing paradigm for prediction of analgesic efficacy in a rat model of sub-chronic knee joint inflammation

Eur J Pain 18 (2014) 213–222

K. Rutten, A. Robens, S.J. Read, T. Christoph

- CFA-induced reductions in burrowing performance reversed by naproxen, pregabalin or morphine
- CFA-induced reductions in burrowing performance not reversed by yohimbine, dexamphetamine or chlordiazepoxide

Challenge 3:

To develop and validate a range of ethologically relevant, pharmacologically validated, pain-related outcome measures that reflect the species specific impact of pain

Improving Internal Validity

Experimental Design, Conduct, Analysis & Reporting

Minimising Bias

Research Paper

PAIN®

157 (2016) 901–909

OPEN

Ensuring transparency and minimization of methodologic bias in preclinical pain research: PPRECISE considerations

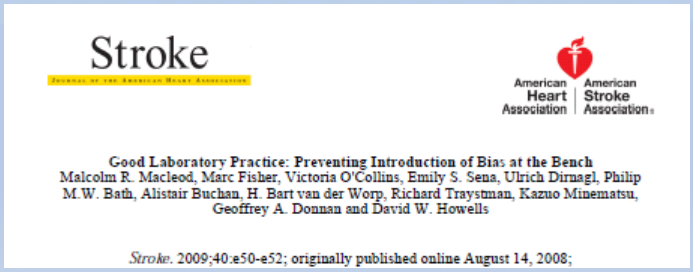
Nick A. Andrews[a,*], Alban Latrémolière[a], Allan I. Basbaum[b], Jeffrey S. Mogil[c], Frank Porreca[d], Andrew S.C. Rice[e], Clifford J. Woolf[a], Gillian L. Currie[f], Robert H. Dworkin[g,h,i], James C. Eisenach[j], Scott Evans[k], Jennifer S. Gewandter[l], Tony D. Gover[m], Hermann Handwerker[n], Wenlong Huang[o], Smriti Iyengar[p], Mark P. Jensen[q], Jeffrey D. Kennedy[r], Nancy Lee[s], Jon Levine[t,u], Katie Lidster[v], Ian Machin[w], Michael P. McDermott[x], Stephen B. McMahon[y], Theodore J. Price[z], Sarah E. Ross[aa], Grégory Scherrer[bb], Rebecca P. Seal[cc], Emily S. Sena[f], Elizabeth Silva[dd], Laura Stone[ee], Camilla I. Svensson[ff], Dennis C. Turk[gg], Garth Whiteside[hh]

“Good Laboratory Practice”

Experimental Design and Conduct of *In Vivo* Laboratory Experiments

CAMARADES

www.camarades.info


Stroke

American Heart Association | American Stroke Association

Good Laboratory Practice: Preventing Introduction of Bias at the Bench

Malcolm R. Macleod, Marc Fisher, Victoria O'Collins, Emily S. Sena, Ulrich Dirnagl, Philip M.W. Bath, Alistair Buchan, H. Bart van der Worp, Richard Traystman, Kazuo Minematsu, Geoffrey A. Donnan and David W. Howells

Stroke. 2009;40:e50-e52; originally published online August 14, 2008;


Scandinavian Journal of Pain 4 (2013) 58–62

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journal homepage: www.ScandinavianJournalPain.com

ELSEVIER

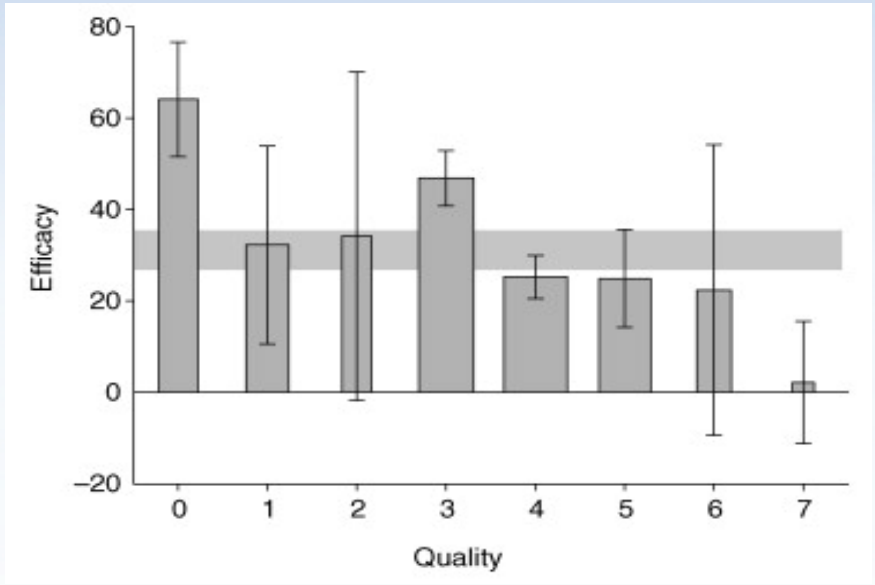
Topical review

Transparency in the reporting of in vivo pre-clinical pain research: The relevance and implications of the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines

Andrew S.C. Rice[a,b,*], Rosemary Morland[a], Wenlong Huang[a], Gillian L. Currie[c], Emily S. Sena[c], Malcolm R. Macleod[c]

GLP Core Domains

- Information about animals
- Sample size calculation
- Explicit inclusion and exclusion criteria
- Randomized allocation to groups
- Allocation concealment
- Blinded assessment and analysis of outcome
- Reporting of animals excluded from analysis
- Declaration and reporting potential conflicts of interest and study funding
- (Date stamped archiving of protocol)



Sena *et al* TiNS2007;30:433

Systematic Review of Chronic Constriction Injury

Currie, Sena, Wodarski, Morland et al

887 included publications
Median reporting quality score 2 out of 8 and IQR (2-1).

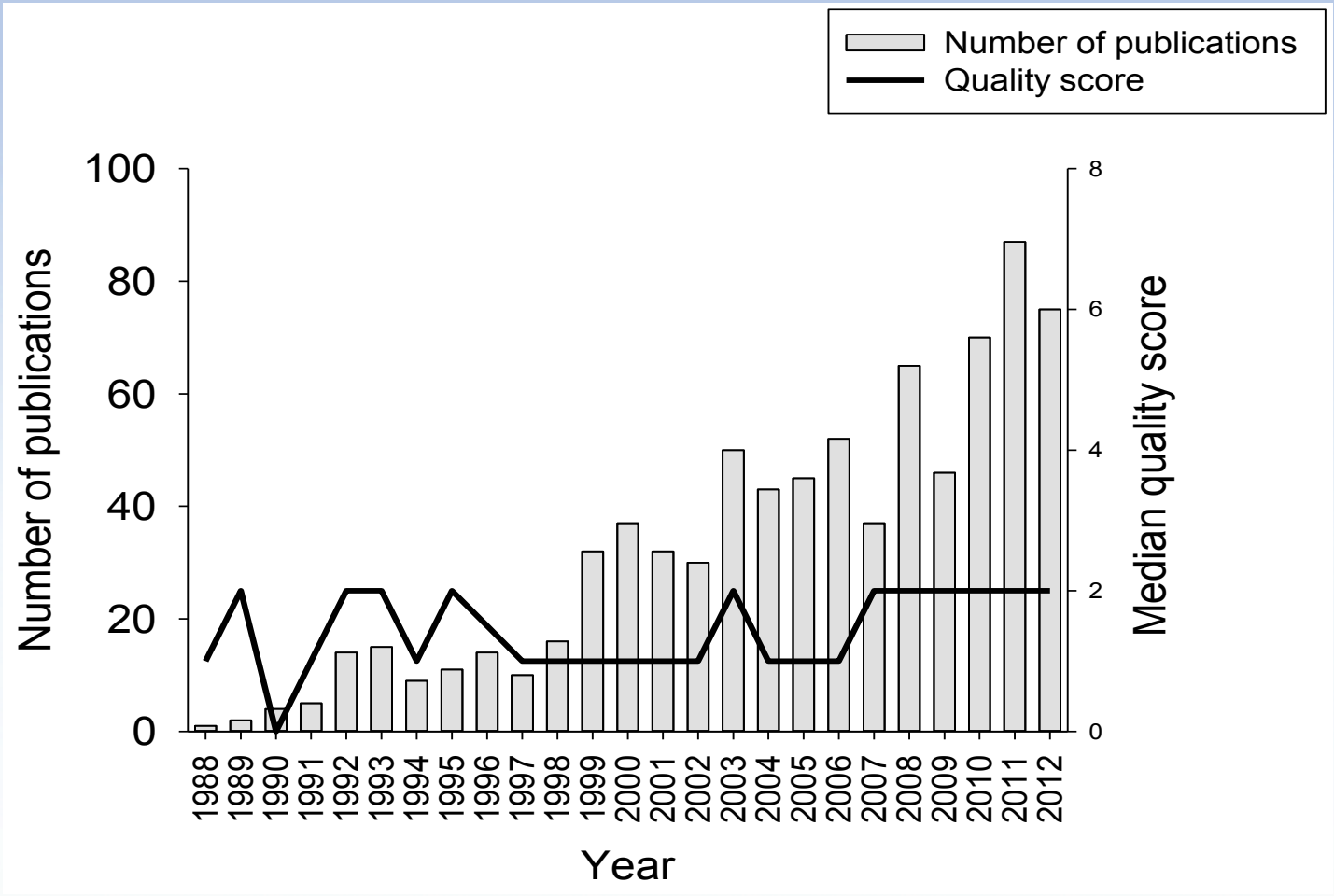
	%	No. of publications /Total
Blinded Assessment of Outcome	**29**	236/805
Allocation concealment	**3**	21/805
Randomisation - Drug	**25**	156/621
Randomisation - Model	**9**	69/805
Animal exclusions	**17**	133/805
Sample Size Calculation	**0.4**	3/805
Animal Welfare Regulations	**88**	706/805
Potential Conflicts of Interest	**12**	99/805

CAMARADES

National Centre for the Replacement Refinement & Reduction of Animals in Research

Imperial College London

Publications and Quality Over Time



Reporting Quality Across Neuropathic Pain Models

%	HIV	Antiretroviral	Alcohol	CIPN	CCI	**Overall quality**
Blinded Assessment of Outcome	50	50	23	46	29	**40**
Allocation concealment	8	0	0	0	3	**2**
Randomisation - Drug	25	43	18	18	25	**26**
Randomisation - Model	25	17	9	12	9	**14**
Animal exclusions	33	25	0	9	17	**17**
Sample Size Calculation	0	0	5	2	0.4	**2**
Animal Welfare Regulations	100	100	96	92	88	**95**
Potential Conflicts of Interest	25	25	14	28	12	**21**

Quality of Experimental Bias Mitigation In Animal Studies of Pain

Rice *et al* Pain 2008;139:241-5

- Located 14 reports in PAIN vols 128-30 (2007) which estimated pharmacological efficacy in an animal model

- Scored with modified Jadad tool[1] that assesses presence and quality of:

  - Randomisation
  - Blinding
  - Reporting of withdrawals/dropouts
  - Power calculation

  - Max. score 7
  - $\geq$ 5/7 required for inclusion in clinical systematic review

Results:

- 5/14 (36%) – described as "blinded"
- 4/14 (29%) – described as "randomised"
- 1/14 (7%) - reported withdrawals/ dropouts
- 0/14 (0%) - described a power calculation

- Modified Jadad score:
  - 13/14 – scored 0/7
  - 1/14 – scored 1/7
  - 0/14 - scored >1/7

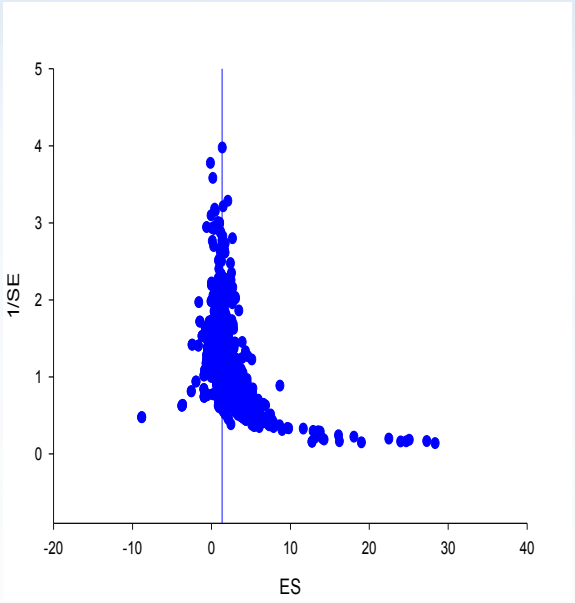
Re-analysis of data from 125 animal studies (Kontinen & Meerk 2003):

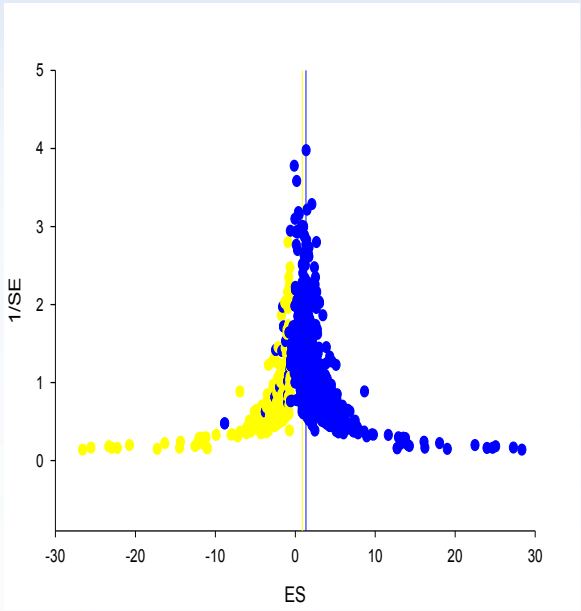
- 29% described as "randomised"
- 28% described as "blinded"

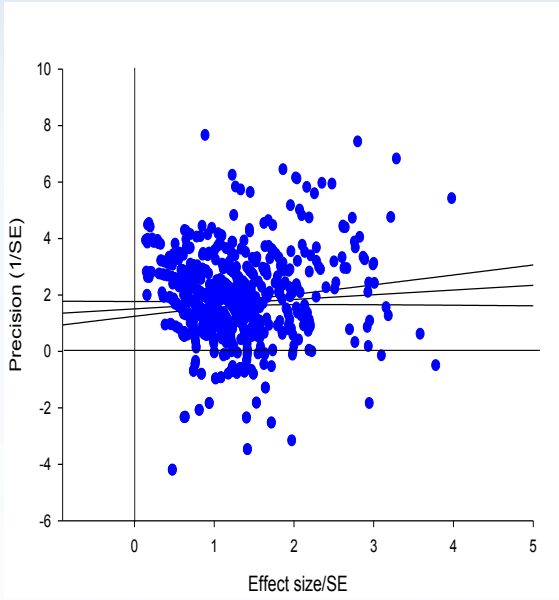
Publication Bias - Pre-Clinical Studies

- **736 original comparisons for Chemotherapy Induced Neuropathy drug intervention experiments**
- **Trim and fill analysis suggests 185 theoretical 'missing' comparisons**

- **Original global estimate effect size 1.35 SMD Units [1.25-1.44]**
- **Adjusted global estimate effect size 0.88 [0.77-0.98]**
- **53% overestimation of efficacy**





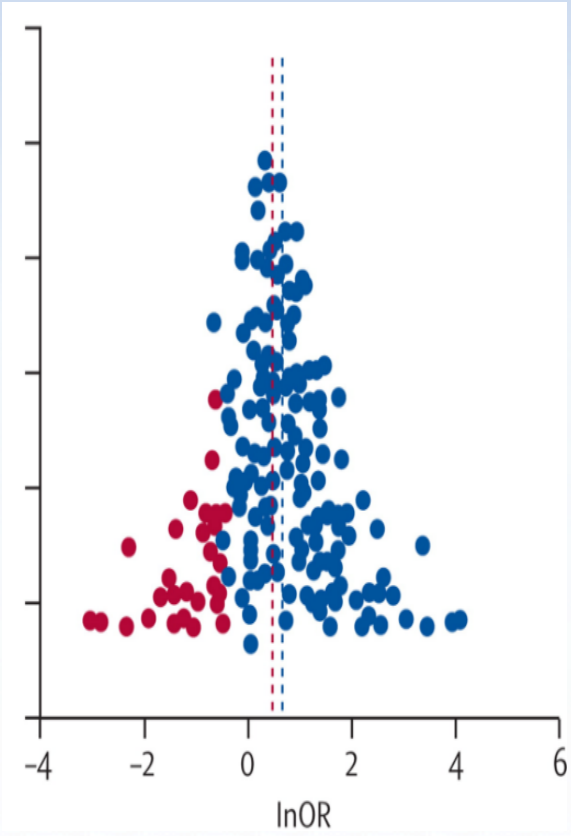


Gillian Currie

Finnerup et al Lancet Neurology 2015;14:162

Publication Bias – Clinical Trials

- 191 published reports and 21 unpublished studies in clinical trials.gov registry
- Trim and Fill analysis suggests 34 theoretical missing studies
- 10% overestimation of efficacy
- Studies in peer-reviewed journals reported greater effects than unpublished studies

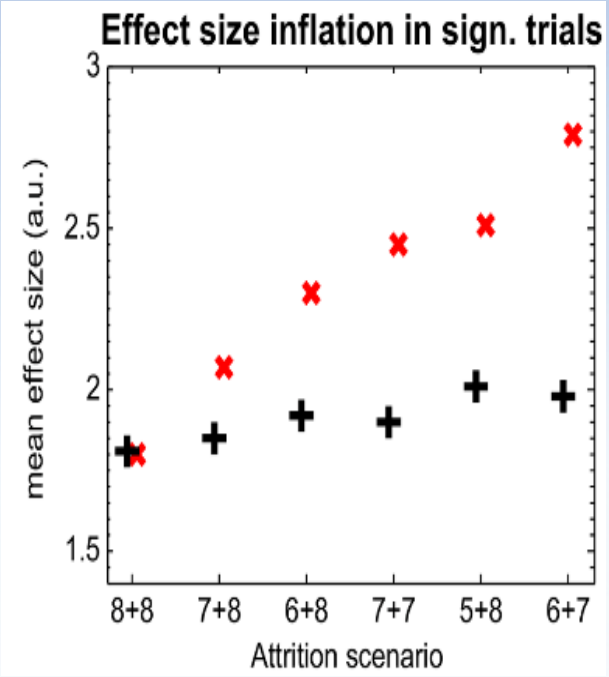


	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)	982
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10·6 (7·4–18·8)	70¶
Botulinum toxin A	4	137	42/70	4/67	1·9 (1·5–2·4)	678

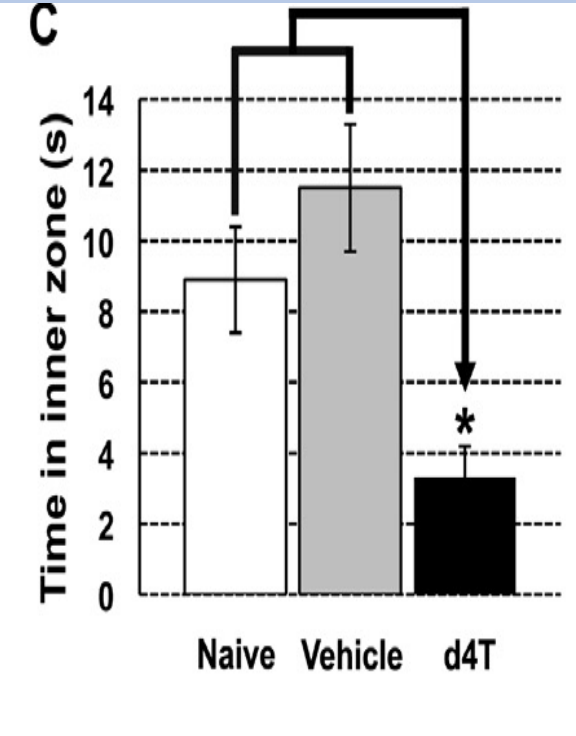
Attrition (loss of animals from analysis) Bias

Holman et al PLoS Biol 2016;14:e1002331

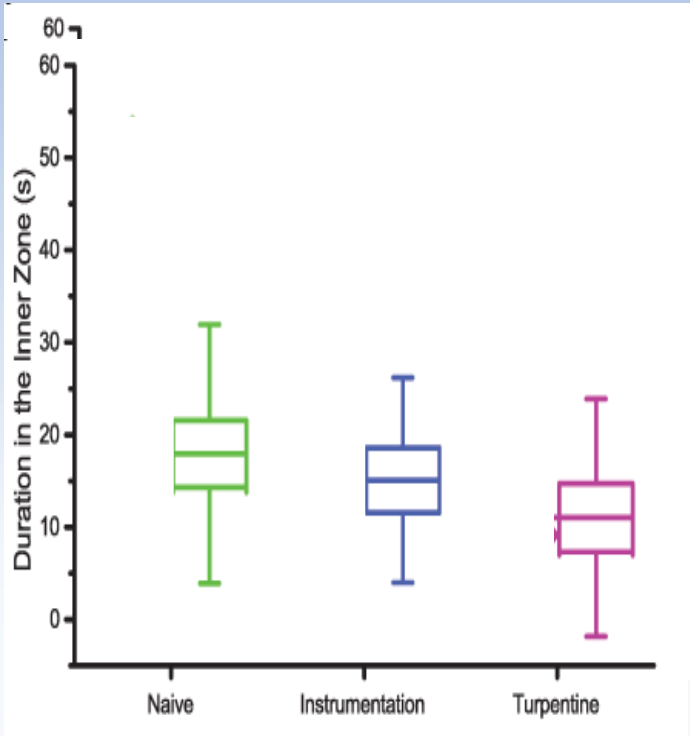
- Simulation of:
  - Random attrition **+** = reduced [already low] statistical power and therefore increase risk of false negatives
  - Biased attrition (targeted exclusion of outliers) exclusion **X** = dramatically increased apparent effect size the probability of false positive results
- Meta-analysis of stroke and cancer models studies show attrition is rarely reported
  - A priori inclusion/exclusion criteria
  - "CONSORT-type" Flow chart



Presentation of Data



Huang et al PAIN 2013;154:560



Morland RH et al. F1000Research 2015, 4:109

Transparency of Publications

www.nc3rs.org.uk/arrive-guidelines

How can you use the ARRIVE guidelines?

The guidelines can be used when reporting research. In brief, the ARRIVE guidelines include the following:

Title

1. Accurate & concise description

Abstract

2. Background, objectives, methods, key findings and conclusions

Introduction

3. Background

4. Objectives

Methods

5. Ethical statement

6. Study design (blinding/randomisation)

7. Experimental procedures (How? When? Where? Why?)

8. Experimental animals (species, sex, weight)

9. Housing and husbandry

10. Sample size

11. Allocation experimental groups

12. Experimental outcomes

13. Statistical methods

Results

14. Baseline Data

15. Numbers Analysed

16. Outcomes & estimation

17. Adverse events

Discussion

18. Interpretation & implications

19. Generalisability and translation

20. Funding

NC 3Rs

For a full description, see the 20-point check list at www.nc3rs.org.uk/ARRIVE

ARRIVE

National Institute of Neurological Disorders and Stroke

www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf

Experimental design:

- Rationale for the selected models and endpoints (animal and/or cellular)
- Adequacy of the controls
- Route & timing of intervention delivery / dosing
- Justification of sample size, including power calculation
- Statistical methods used in analysis and interpretation of results

Minimizing bias:

- Methods of blinding (allocation concealment and blinded assessment of outcome)
- Strategies for randomization and/or stratification
- Reporting of data missing due to attrition or exclusion
- Reporting of all results (negative and positive)

Results:

- Independent validation/replication, if available
- Robustness and reproducibility of the observed results
- Dose-response results
- Verification that interventional drug or biologic reached and engaged the target

Interpretation of results:

- Alternative interpretations of the experimental data
- Relevant literature in support or in disagreement with the results
- Discussion of effect size in relation to potential clinical impact
- Potential conflicts of interest

Landis et al Nature 2012;490(7419):187-191.

Courtesy Shai Silberberg NINDS

Transparency of Reporting Open Access to Single Animal Level Raw Data

+AllTrials

www.alltrials.net

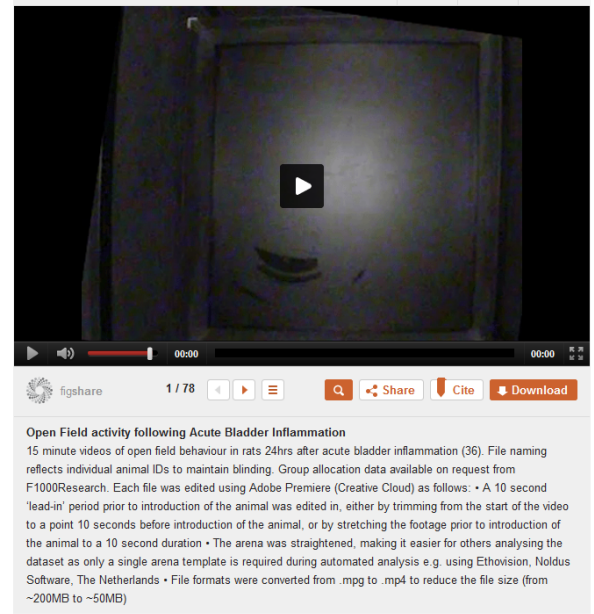
F1000Research F1000Research 2015, 4:109 Last updated: 09 SEP 2015

CrossMark click for updates

RESEARCH ARTICLE

Short-term effect of acute and repeated urinary bladder inflammation on thigmotactic behaviour in the laboratory rat [version 1; referees: 3 approved]

Rosemary H Morland[1], Amparo Novejarque[1], Wenlong Huang[1], Rachel Wodarski[1], Franziska Denk[2], John D Dawes[3], Tim Pheby[1], Stephen B McMahon[2], Andrew SC Rice[1]



- Technically possible with digital data capture and on-line publication
- Independent scrutiny of data
- Independent replication of analyses
- Animal level meta-analysis
- Conduct of alternative analyses
- *In silico* testing and refinement of novel analysis paradigms

Challenge 4:

To develop adequate design, conduct, analysis and reporting which permit:

a. Assessment of rigour of experiments
b. Meta-analysis
c. Access to all data, including that from sub-sets of animals and "outliers" which may be relevant to heterogeneity

CHALLENGES IN ALIGNING PRE-CLINICAL RESEARCH WITH PRECISION PAIN MEDICINE AGENDA:

1. Develop and validate portfolio of clinically aligned disease models and explore heterogeneity

2. Develop and validate clinically aligned profiling measures

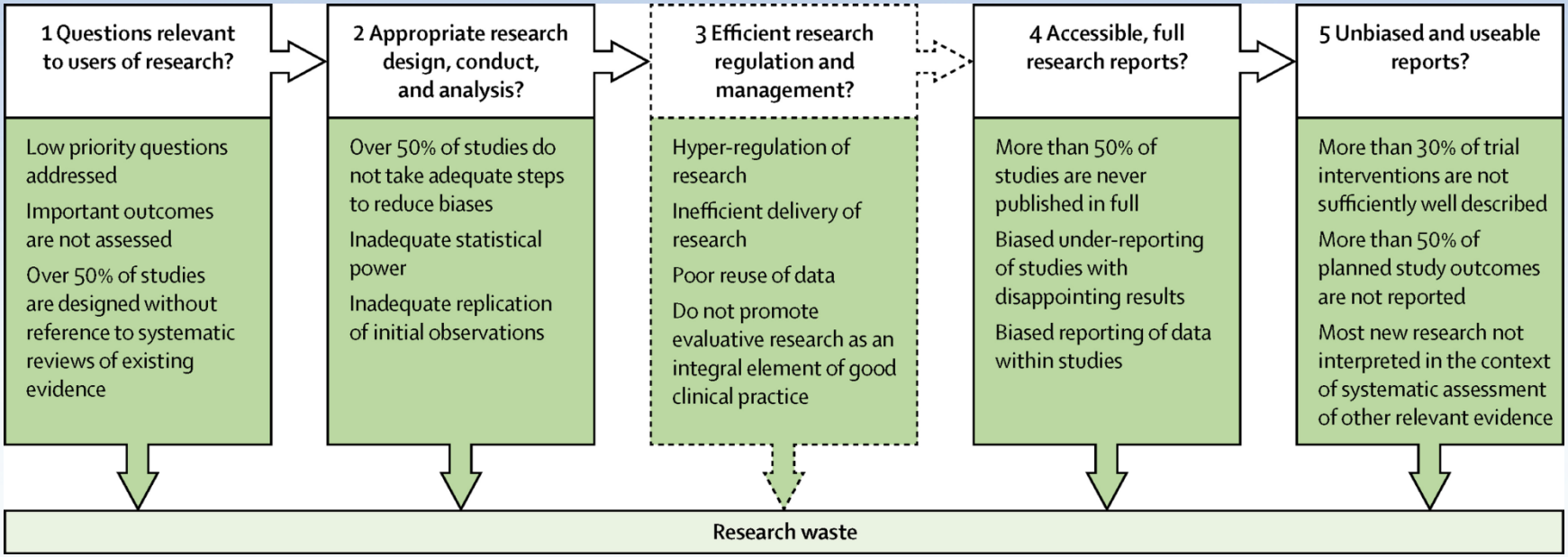
3. Ethologically-relevant, pharmacologically validated, outcome measures and explore heterogeneity

4. Ensure rigour in the design, conduct, analysis and reporting of pre-clinical experiments

Lancet Series on Research Waste 2014

85% Of Biomedical Research Investment Is Wasted - $200 Billion In 2010

Chalmers & Glasziou Lancet 2009; 374:86–89; Lancet Series on Research Waste 2014; Moher, D., et al. Lancet. Online September 28, 2015



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www.researchwaste.ne

THE LANCET

equator network

www.equator-network.org

The London Pain Consortium