# Advancing the Search for Novel Preventive Analgesics

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## ACTION on the Prevention of Chronic Pain after Surgery

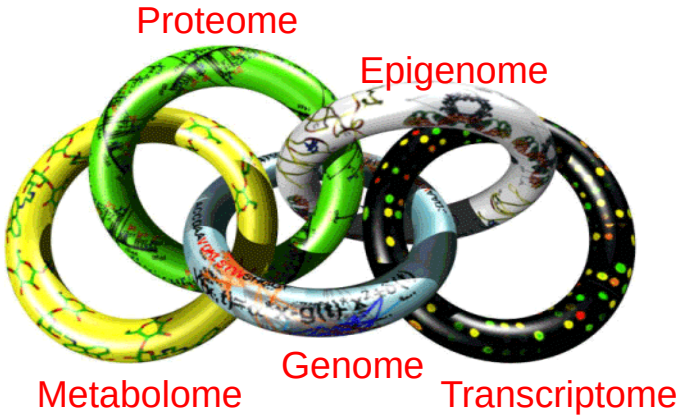
*Public–Private Partnerships, the Future of Analgesic Drug Development*

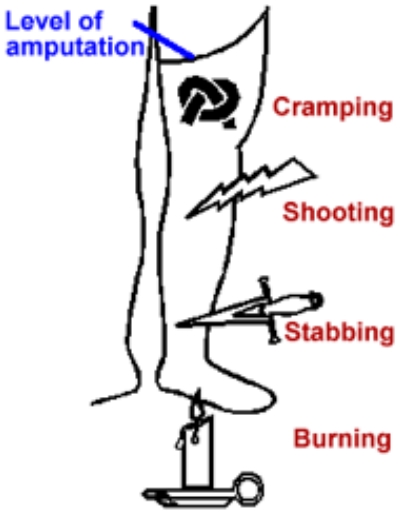
- Clear need for new analgesics
- FDA has never received a marketing application for a drug product that is intended to prevent chronic pain
- “We do not know what an appropriate clinical trial design should look like to provide an accurate and efficient assessment of chronic pain prevention after surgery”
- “We need preclinical models that replicate the complexity of the human condition.”

Anesthesiology 2010; 112:509–10

# VIPER – Veterans Integrated Pain Evaluation Research

## A comparative biology approach to chronic post-nerve injury pain




Duke Anesthesiology

# Prevention of Chronic Postsurgical Pain

## *The Ongoing Search for the Holy Grail of Anesthesiology*

S. P. Cohen and S. N. Raja

Anesthesiology, V 118 • No 2 February 2013

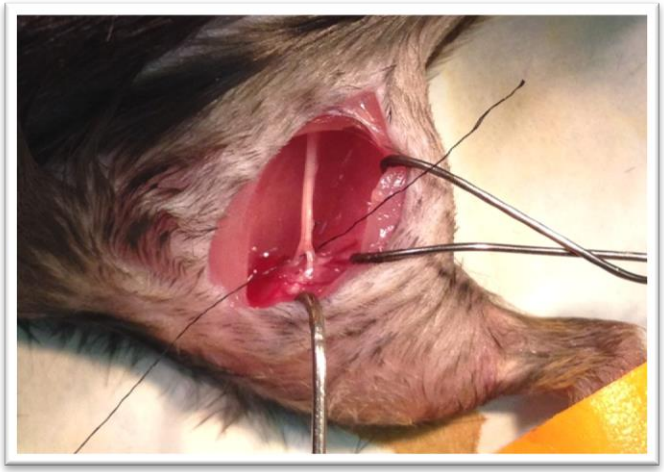
. . . we are still left with the seemingly Sisyphean task of how to prevent CPSP, and the question of whether or not the Holy Grail of preventive analgesia is even obtainable.

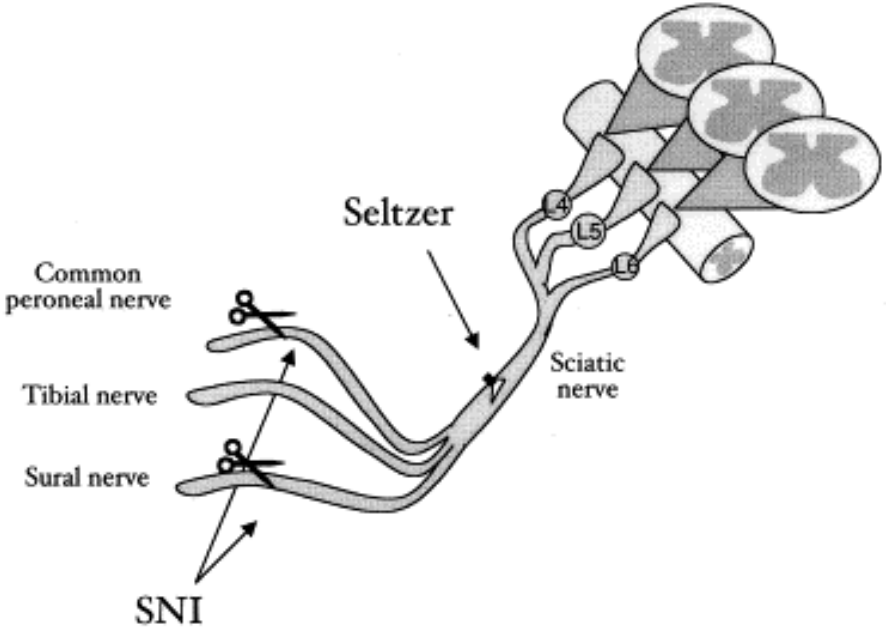
# Why have promosing preclinical analgesics failed in human trials?

- Limitations of preclinical models
- Limited understanding of the transition from acute to chronic pain
- Limitations of clinical trial design

# Problems with animal studies

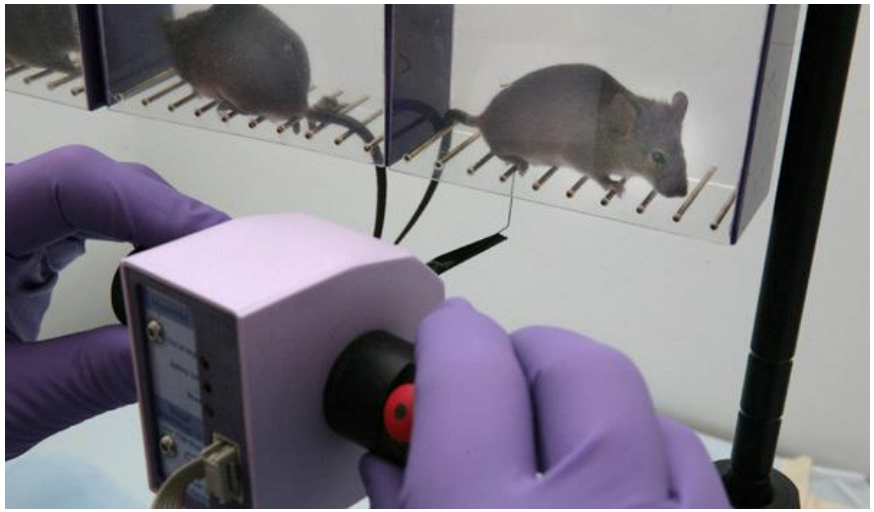
- Mismatch between lesion in animal and humans
  - 75% of RTCs target polyneuropathy and herpetic neuralgia while most of the animal studies use peripheral nerve injury.

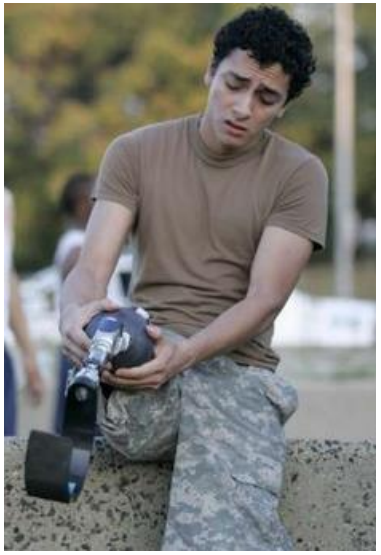




# Problems with animal studies

- Outcome measures
  - Animal studies measure evoked pain
  - Humans with neuropathy complain most of spontaneous pain





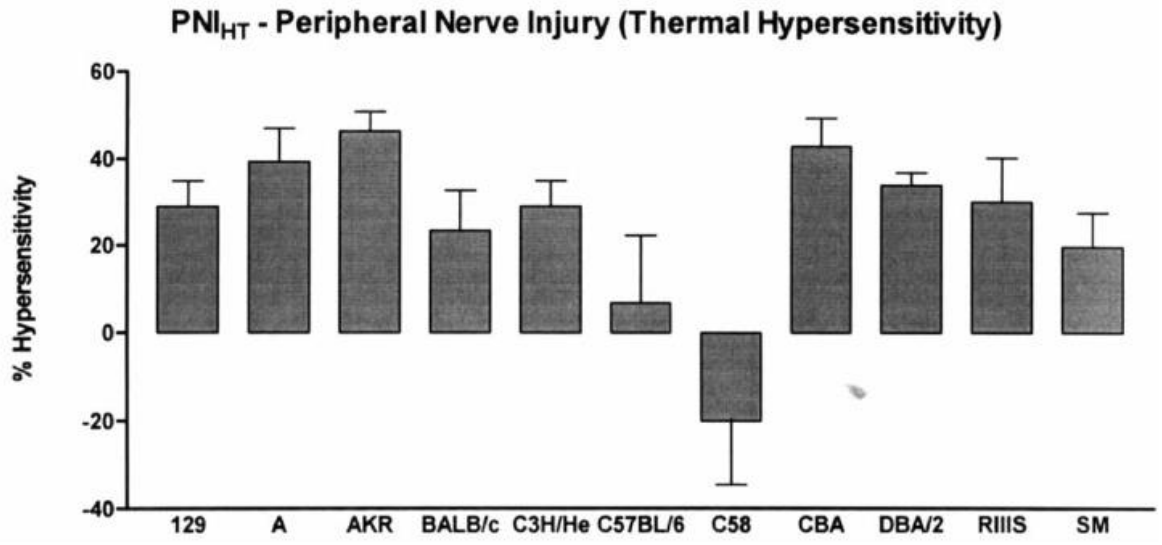
# Problems with animal studies

- Timing
  - Most human RTCs include patients with chronic pain of multiple year duration
  - Most animal treatment data is collected within 3 weeks of the pain causing lesion

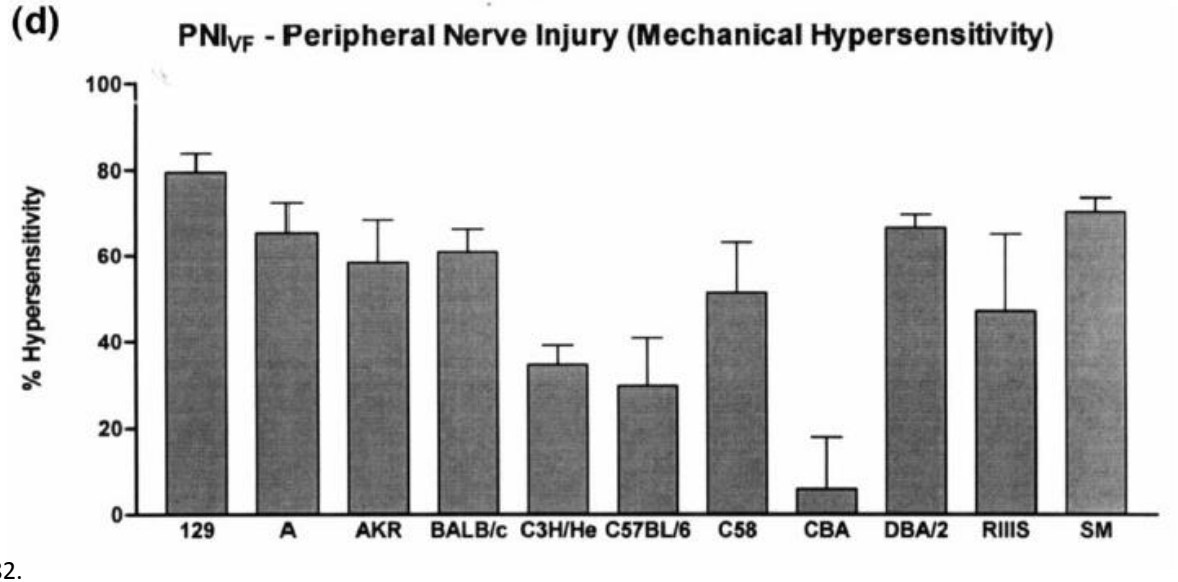
# Problems with animal studies

- Incidence
  - All animals with sciatic nerve injury develop dramatic mechanical hypersensitivity
  - About 1/10 patients with significant nerve injury or herpes zoster infection develop severe chronic neuropathic pain

# Strain differences in mouse pain




(d)

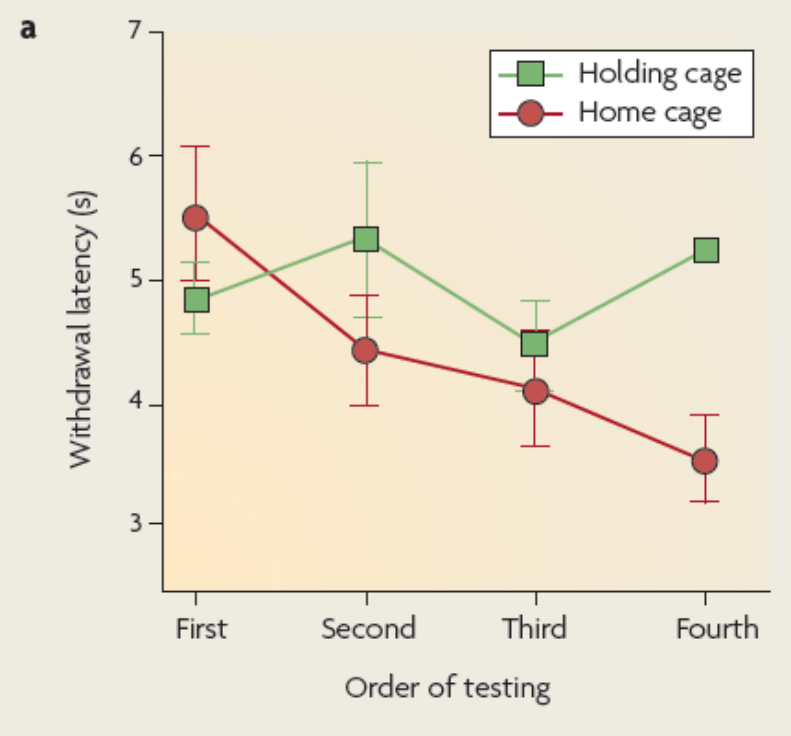



7. Mogil, Pain (80) 1999. 67-82.

# Problems with animal studies

- Age and health of participant
  - Most animal studies use young, healthy, genetically identical animals
  - Most humans with chronic neuropathy are not young and have medical comorbidities.

# Social communication and pain




6. Mogil, Nature Reviews Neuroscience, Vol 10 April 2009.

# Methodological issues

- Analysis of 271 publicly funded animal studies in US and UK
  - 41% of studies did not state the objective of the study and number of animals used
  - 87% did not randomise
  - 86% did not utilize blinded observers of qualitative outcomes
  - 30% did not describe statistical methods

Kilkenny et al. PLOSone, November 2009, Vol.4 Issue 11.

# Complex Pain states

- “Human clinical pain involves emotional and cognitive modulatory factors not often (or not effectively) measured in animals.”

  - Jeff Mogil – Pain Research Bulletin 2011

- Mice do not seem to be particularly affected by chronic pain.

# Hooke’s dog thoracotomy

**"of more cruelty than pleased me.**

# The Three R's[2]

- Replacement
  - Substitute with least "sentient" animal possible
- Reduction
  - Limit the number of experimental animals
- Refinement
  - Decrease severity of experimental procedure

2. Russell and Burch, The Principles of Humane Experimental Technique. 1959.c

# ARRIVE guidelines

| | Item | Recommendation (Kilkenny *et al.*, 2010) |
|---|---|---|
| **TITLE** | 1 | Provide as accurate and concise a description of the content of the article as possible. |
| **ABSTRACT** | 2 | Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study. |
| **INTRODUCTION** | | |
| **Background** | 3 | a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.<br>b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology. |
| **Objectives** | 4 | Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. |
| **METHODS** | | |
| **Ethical statement** | 5 | Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research. |
| **Study design** | 6 | For each experiment, give brief details of the study design including:<br>a. The number of experimental and control groups.<br>b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when).<br>c. The experimental unit (e.g. a single animal, group or cage of animals).<br>A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out. |
| **Experimental procedures** | 7 | For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example:<br>a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).<br>b. When (e.g. time of day).<br>c. Where (e.g. home cage, laboratory, water maze).<br>d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used). |

# Preclinical model considerations

- We must be more critical in our reading of animal research.
- Should animal studies be limited or more regulated?
- 25 million mice are used each year in research.

# Future directions in animal preclinical models

- Multiple strains of male and female mice for each experiement.
- Heavier reliance on measures of spontaneous pain.
- Validation across species.
- Sophisticated video tracking in home cage.

# Mechanisms behind the transition from acute to chronic pain

# Persistent Post-operative Pain

| Procedure | Chronic pain | >5/10 Severe Pain | Surgeries per year |
|---|---|---|---|
| Amputation | 30 - 50% | 5 -10% | 159,000 |
| Mastectomy | 20 - 30% | 5 -10% | 479,000 |
| Thoracotomy | 30 -40 % | 10% | ~100,000 |
| Inguinal hernia | 10 % | 2 – 4 % | 609,000 |
| CABG | 30 -50 % | 5 - 10% | 598,000 |

Kehlet et al, 2006

# Persistent Post-operative Pain

| Surgery | # Studies | Med (range) | Time Post Surgery | Conservative PPSP % (Range) | Liberal PPSP % (Range) |
|---|---|---|---|---|---|
| Thoracic | 44 | 86(23–1080) | 2 m – 12 y | 34.5 (21–52) | 37 (23.5–52) |
| Breast | 53 | 106(22-3253) | 2 m –35 y | 31 (21.5–47.3) | 41 (24.3–49) |
| Abdominal | 6 | 86 (22–286) | 1–10 y | 11 (4.7–18) | 11.5(3.5–18) |
| Donor neph | 12 | 75 (53–359) | 1.5 m - 15y | 9.6 (3.2–25) | 21.3(3.7–33) |
| Gyn | 13 | 90 (36–1135) | 3-24 m | 13.7 (7.8–17.3) | 13.7(11.5-34) |
| Prostate | 8 | 95 (24–179) | 2.5-6 m | 14 (8–36) | 21 (10.4–36) |
| Hernia | 89 | 266(22-5524) | 1.5 m – 12 y | 7 (2.5–19) | 12 (4.4–23.6) |
| THA/TKA | 13 | 142(20-7230) | 4 m - 8 y | 19.8(11.7–27.7) | 27(12.5–39.1) |
| Iliac crest bone harvest | 29 | 94.5(10–414) | 3 m -13 y | 18.7(12.5–28.3) | 23.5(14-35.1) |
| Varicose vein | 6 | 83.5 (35–126) | 3 m -11y | 4.7 (4–13) | 4.7 (4–13) |

Haroutiunian S.Pain.154;95–102:2013

# Initial preventive analgesia strategy

- Hypothesis: Aberrant nociceptor conduction at the time of nerve injury leads to long-term potentiation.

- Solutions:
  - Block nociceptor conduction (nerve blockade)
  - Reduce NMDA receptor signaling (ketamine)
  - Reduce neurotransmitter release at glutamatergic synapses (gabapentin)

# Trials of single modality prevention

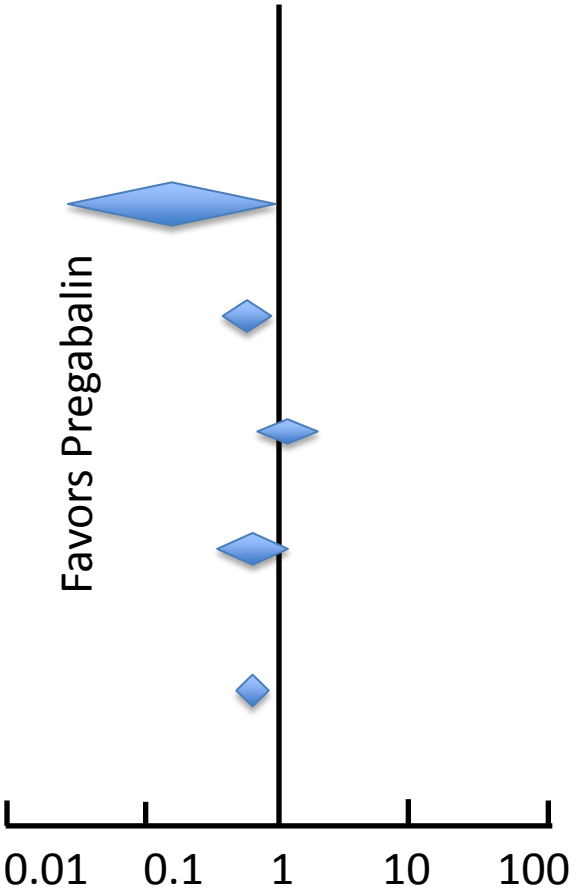
| Study | Number of Patients | Single Blinded RCT | Intervention tested for significance | Significant reduction in chronic pain (per study authors) |
|---|---|---|---|---|
| **Amputation** | | | | |
| Fisher et al | 11 | No | Continuous sciatic nerve sheath block | Yes |
| Borghi et al | 71 | No | Prolonged continuous regional analgesia | Yes |
| Nikolajsen et al. | 60 | Yes | Preemptive vs postoperative epidural analgesia | No |
| Karanikolas et al. | 65 (randomized to 5 groups) | Yes | Perioperative epidural analgesia vs. Perioperative IV PCA* | No* |
| Pinzur et al. | 21 | Yes | Continuous perineural bupivacaine infusion | No |
| Hayes et al | 45 | Yes | 72 hr ketamine infusion | No |
| Nikolajsen et al | 46 | Yes | 30 days gabapentin | No |
| Schley et al | 19 | Yes | 4 weeks memantine | Yes at 6 months<br>No at 12 months |

# Trials of single modality prevention

| Study | Number of Patients | Single Blinded RCT | Intervention tested for significance | Significant reduction in chronic pain (per study authors) |
|---|---|---|---|---|
| **Thoracotomy** | | | | |
| Tiippana et al. | 114 | No | Thoracic Epidural | Yes |
| Senturk et al | 69 (divided into 3 groups) | Yes | Thoracic Epidural | Yes |
| Ju et al | 107 | Yes | Thoracic epidural vs. intercostal cryoanalgesia | No |
| Katz et al | 30 | Yes | Intercostal nerve clock | No |
| Lu et al | 105 (divided into 3 groups) | Yes | Thoracic epidural | Yes |
| Duale et al | 86 | Yes | Ketamine infusion | No |
| Suzuki et al | 50 | Yes | Ketamine infusion | No (at 6 months) |
| Kinney et al | 120 | Yes | Gabapentin | No |

# Pregabalin versus placebo:
# **Incidence of pain at 3 months**

| **Surgical Population** | **Risk Ratio** |
|---|---|
| Cardiac Surgery | 0.14 |
| Total Knee Arthroplasty | 0.64 |
| Spine Surgery | 1.07 |
| Thyroidectomy | 0.77 |
| Total | 0.70 |

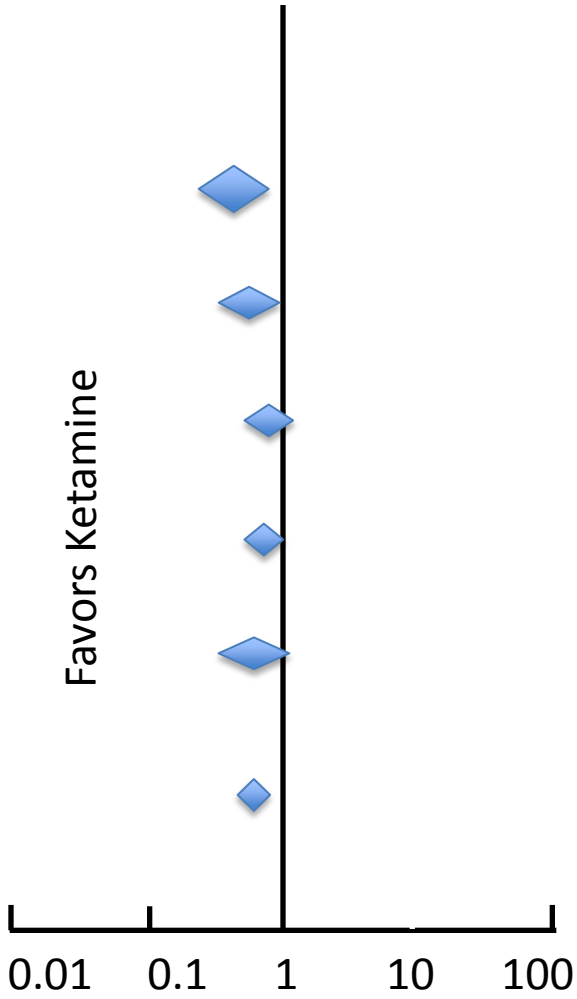



**Systematic Review**

Chaparro et al, 2013

# Ketamine versus placebo:
# **Incidence of pain at 6 months**


| Surgical Population | Risk Ratio |
|---|---|
| Abdominal or Pelvic Surgery | 0.4 |
| Amputation | 0.66 |
| Breast Surgery | 0.87 |
| Orthopedic Surgery | 0.65 |
| Thoracotomy | 0.55 |
| Total | 0.63 |




Systematic Review

Chaparro et al, 2013

# Neuroinflammatory response to nerve injury

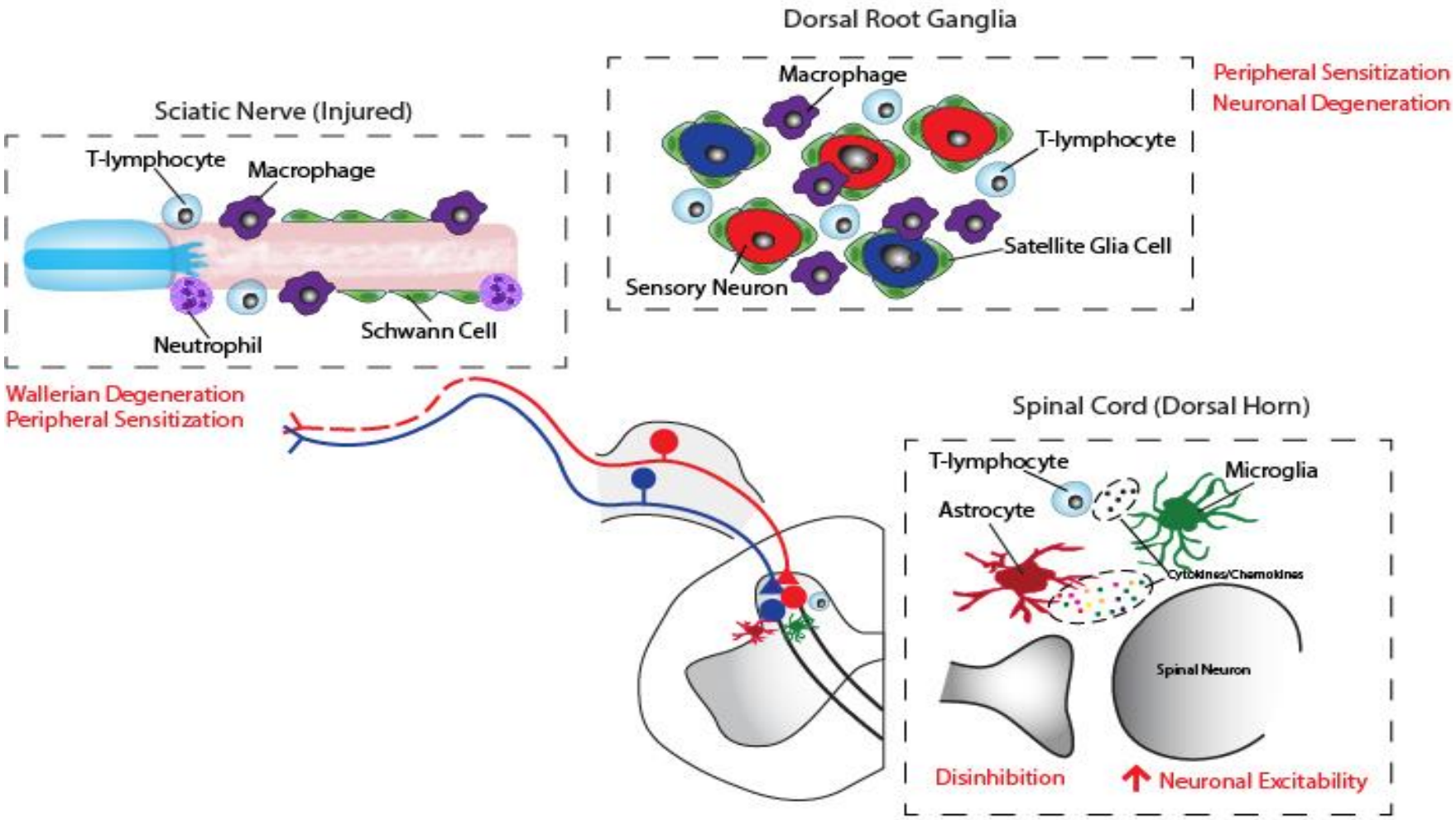



Figure - Alexander Chamessian

# Neuroplastic response to nerve injury

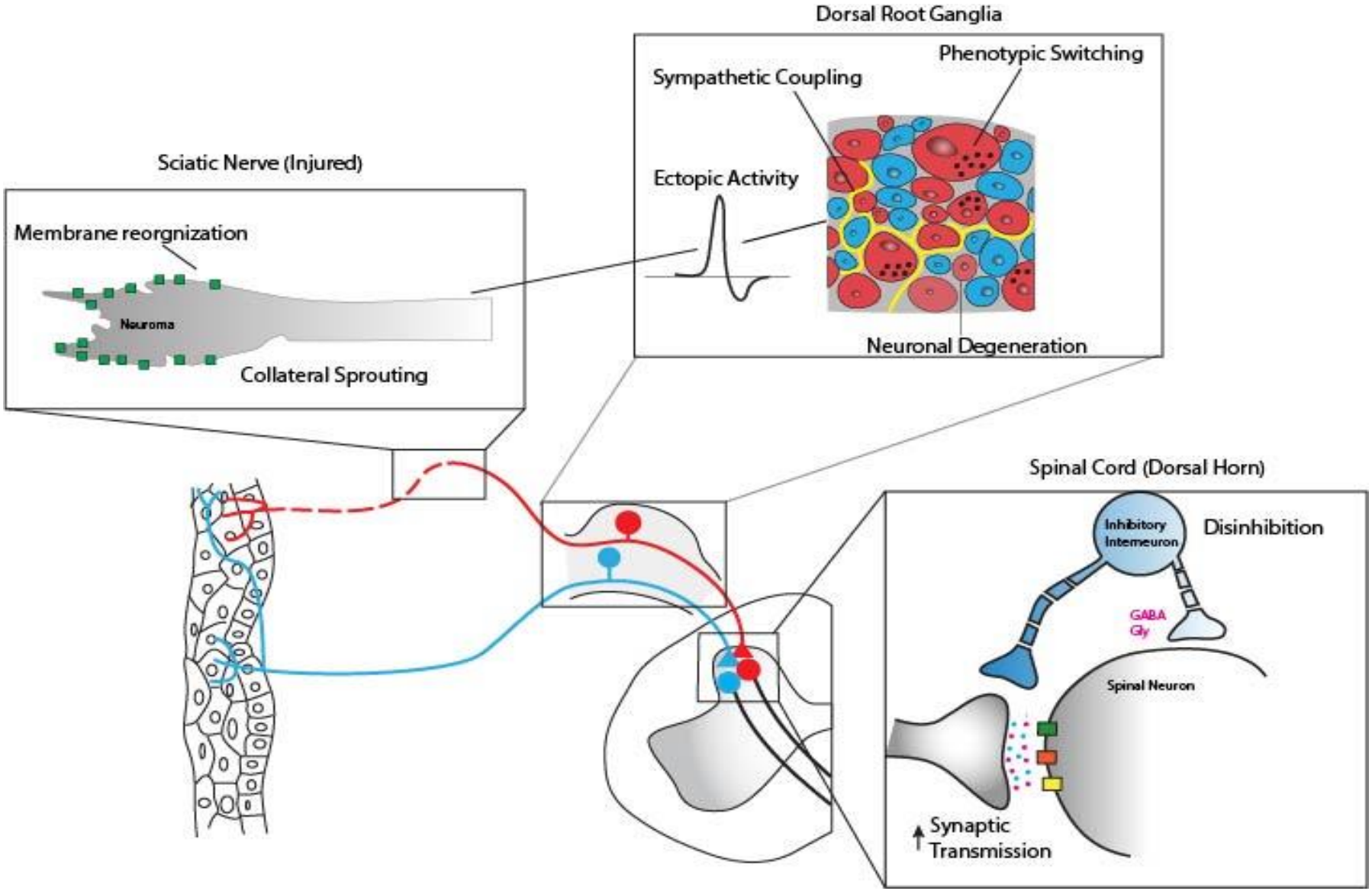
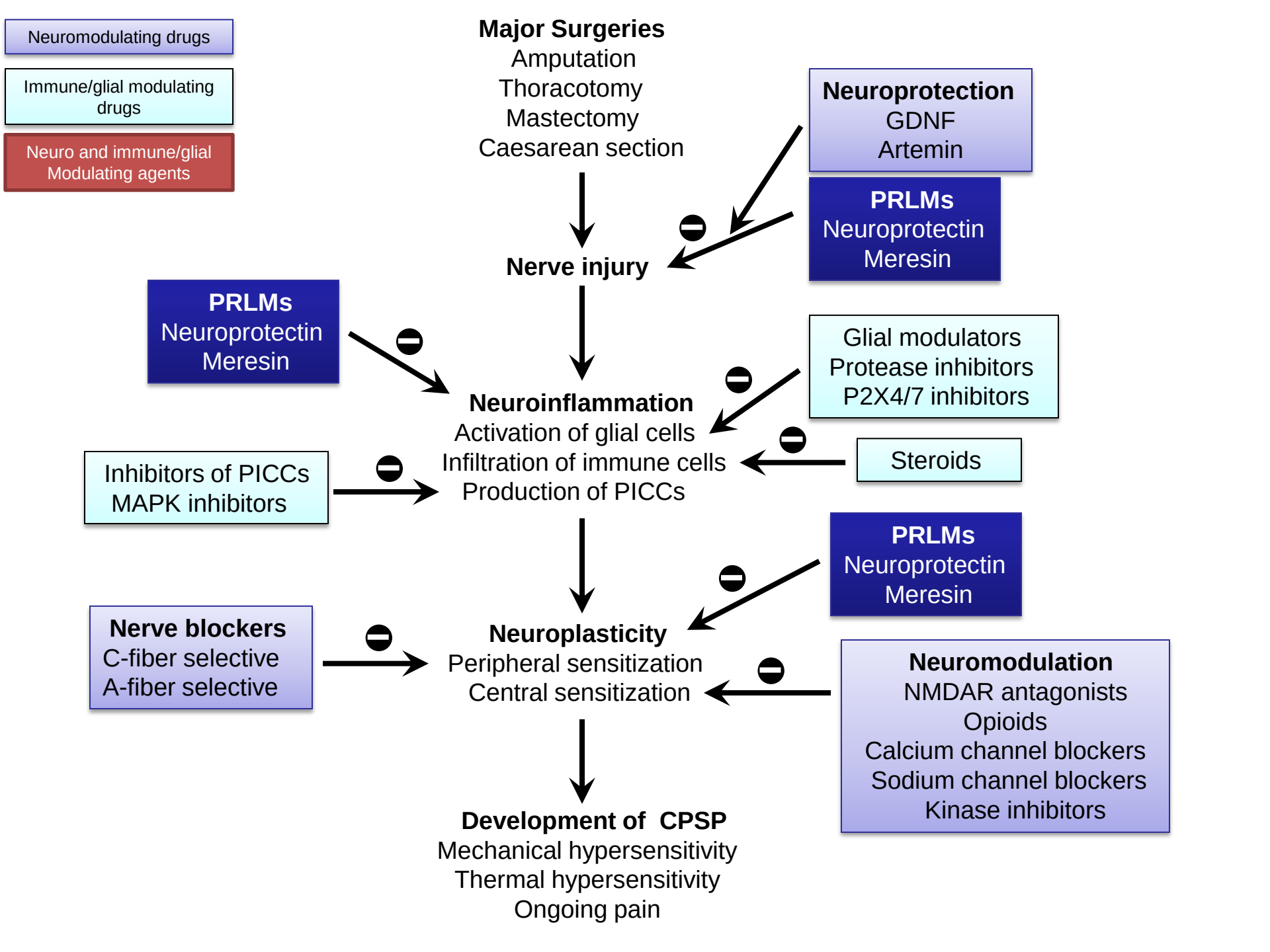



Figure - Alexander Chamessian


Neuromodulating drugs
Immune/glial modulating drugs
Neuro and immune/glial Modulating agents
Major Surgeries
Amputation
Thoracotomy
Mastectomy
Caesarean section
Neuroprotection
GDNF
Artemin
PRLMs
Neuroprotectin
Meresin
Nerve injury
PRLMs
Neuroprotectin
Meresin
Glial modulators
Protease inhibitors
P2X4/7 inhibitors
Neuroinflammation
Activation of glial cells
Infiltration of immune cells
Production of PICCs
Steroids
Inhibitors of PICCs
MAPK inhibitors
PRLMs
Neuroprotectin
Meresin
Nerve blockers
C-fiber selective
A-fiber selective
Neuroplasticity
Peripheral sensitization
Central sensitization
Neuromodulation
NMDAR antagonists
Opioids
Calcium channel blockers
Sodium channel blockers
Kinase inhibitors
Development of CPSP
Mechanical hypersensitivity
Thermal hypersensitivity
Ongoing pain

# Clinical trial limitations

- Recent RCTs did not show efficacy of first line agents for chronic neuropathic pain.

- RCTs have failed to show efficacy of drugs that were very promising in preclinical studies.

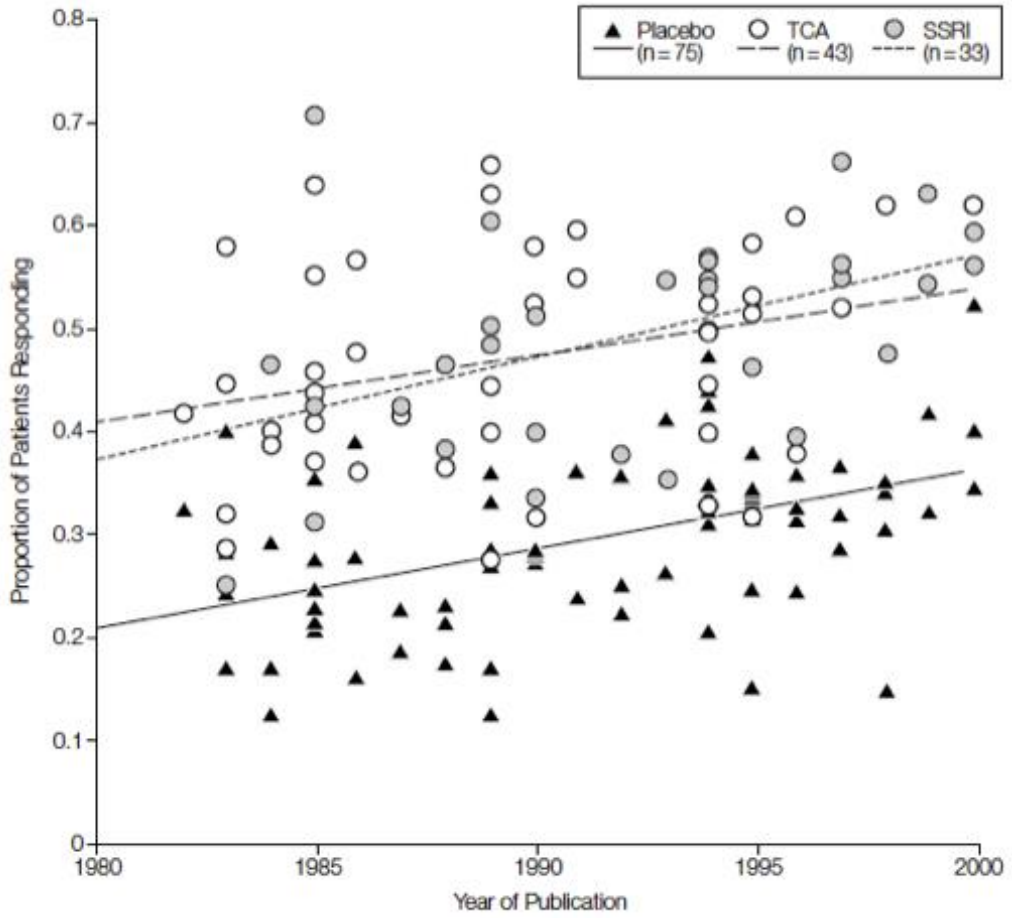
# Reasons for Trial Failure

Enrollee factors

- Patients enrolled have already failed multiple analgesics.
- Patient expectations are higher
- Shift to private, for-profit study sites
- Professional patients
- Less stringent patient selection at the end of a study

# Placebo Effect Increasing

**Figure.** Proportion of Patients Assigned to Placebo, Tricyclic Antidepressants (TCAs), and Selective Serotonin Reuptake Inhibitors (SSRIs) Who Showed a 50% or Greater Improvement in Hamilton Rating Scale For Depression Score by Year of Publication



# Reasons for Trial Failure

- Poorly defined pain syndromes

# Progress

## Assay sensitivity and study features in neuropathic pain trials

### An ACTTION meta-analysis

**Objective:** Our objective was to identify patient, study, and site factors associated with assay sensitivity in placebo-controlled neuropathic pain trials.

**Methods:** We examined the associations between study characteristics and standardized effect size (SES) in a database of 200 publicly available randomized clinical trials of pharmacologic treatments for neuropathic pain.

**Conclusions:** Our analyses have examined potentially modifiable correlates of study SES and shown that a minimum pain inclusion criterion of 40 or above on a 0 to 100 scale is associated with a larger SES. These data provide a foundation for investigating strategies to improve assay sensitivity and thereby decrease the likelihood of falsely negative outcomes in clinical trials of efficacious treatments for neuropathic pain. *Neurology*® 2013;81:67–75

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www.elsevier.com/locate/pain

# Discrepancies between registered and published primary outcome specifications in analgesic trials: ACTTION systematic review and recommendations

Shannon M. Smith [a,*], Anthony T. Wang [b], Anthony Pereira [a], R. Daniel Chang [a]
Andrew McKeown [a], Kaitlin Greene [c], Michael C. Rowbotham [c], Laurie B. Burke [d], Paul Coplan [e,f]
Ian Gilron [g], Sharon H. Hertz [d], Nathaniel P. Katz [h,i], Allison H. Lin [d], Michael P. McDermott [j]
Elektra J. Papadopoulos [d], Bob A. Rappaport [d], Michael Sweeney [k], Dennis C. Turk [l], Robert H. Dworkin [m]

Thirty percent of the trials contained unambiguous POS discrepancies (eg, **omitting a registered PO from the publication, ''demoting'' a registered PO to a published secondary outcome)**, with a statistically significantly higher percentage of non-industry-sponsored than industry-sponsored trials containing unambiguous POS discrepancies.

At worst, discrepancies could indicate investigator impropriety (eg, registering imprecise PO [''pain''], then publishing whichever pain assessment produced statistically significant results).

# Progress

- A standard database format for clinical trials of pain treatments: an ACTTION–CDISC initiative. Pain, 2013;154:11-14
- Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain, 2013;154:2287-2296
- The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. Journal of Pain, 2014;15:241-249
- Research design considerations for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. Pain, 2014;155:1683-1695
- Reporting of missing data and methods used to accommodate them in recent analgesic clinical trials: ACTTION systematic review and recommendations. Pain, 2014;155:1871-1877
- RReACT goes global: perils and pitfalls of constructing a global open-access database of registered analgesic clinical trials and trial results. Pain, 2014;155:1313-1317.

# Summary

- We've made little progress discovering new analgesics, especially preventive analgesics.
- Modification and standardization of preclinical and clinical trials is vital.
- The multifaceted and extended nature of the immune and neuroplastic response to nerve injury necessitates a long-lasting and multi-modal approach to prevention.