IMMPACT-XIII

Recommendations for Improving Assay Sensitivity in Chronic Pain Clinical trials

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Assay Sensitivity and Drug Development

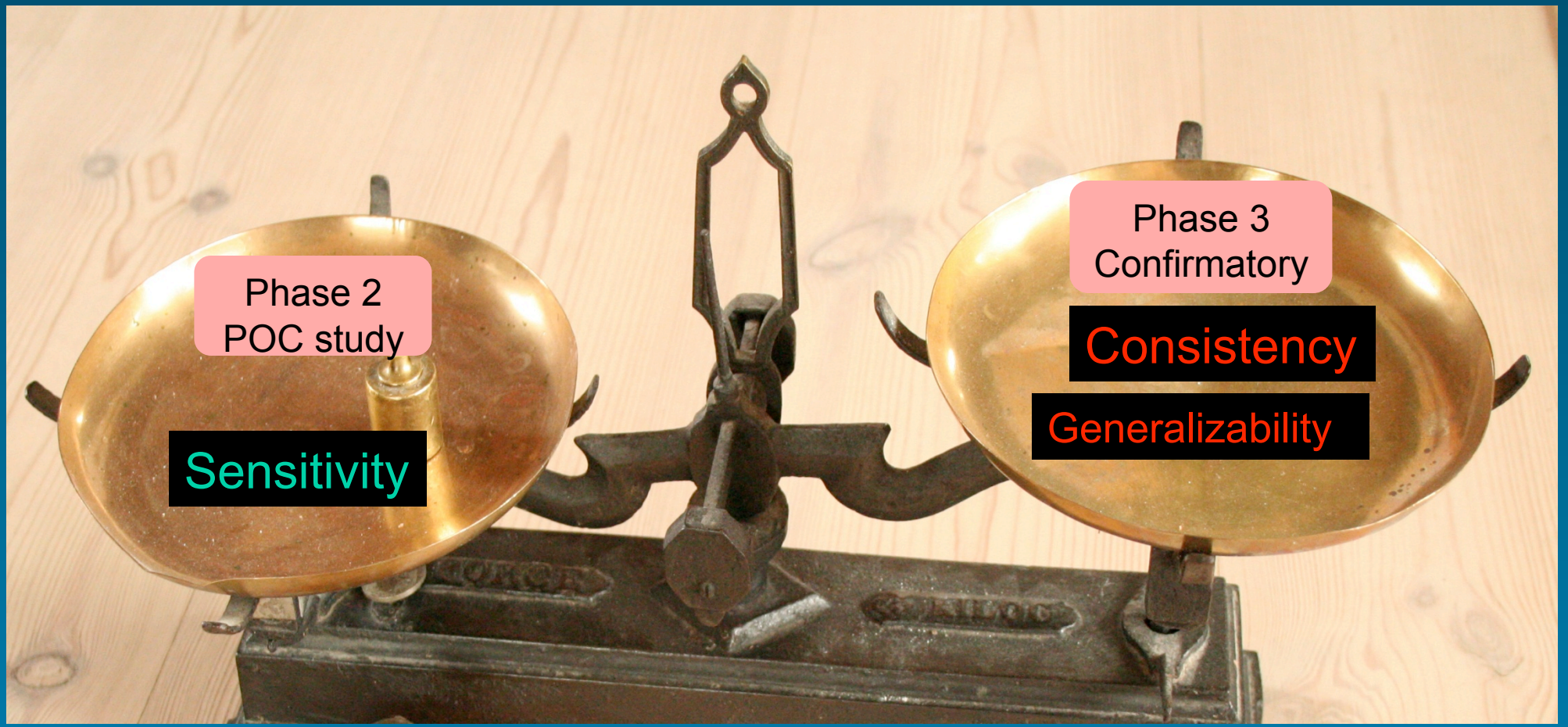
Proof of Concept Studies (Phase 2)- Nat Katz

- Early stage development of a promising compound based on animal models and safety testing
- Goals: Determine potential clinical efficacy and help make an early Go-No Go decision

Confirmatory Studies (Phase 3)- Bob Dworkin

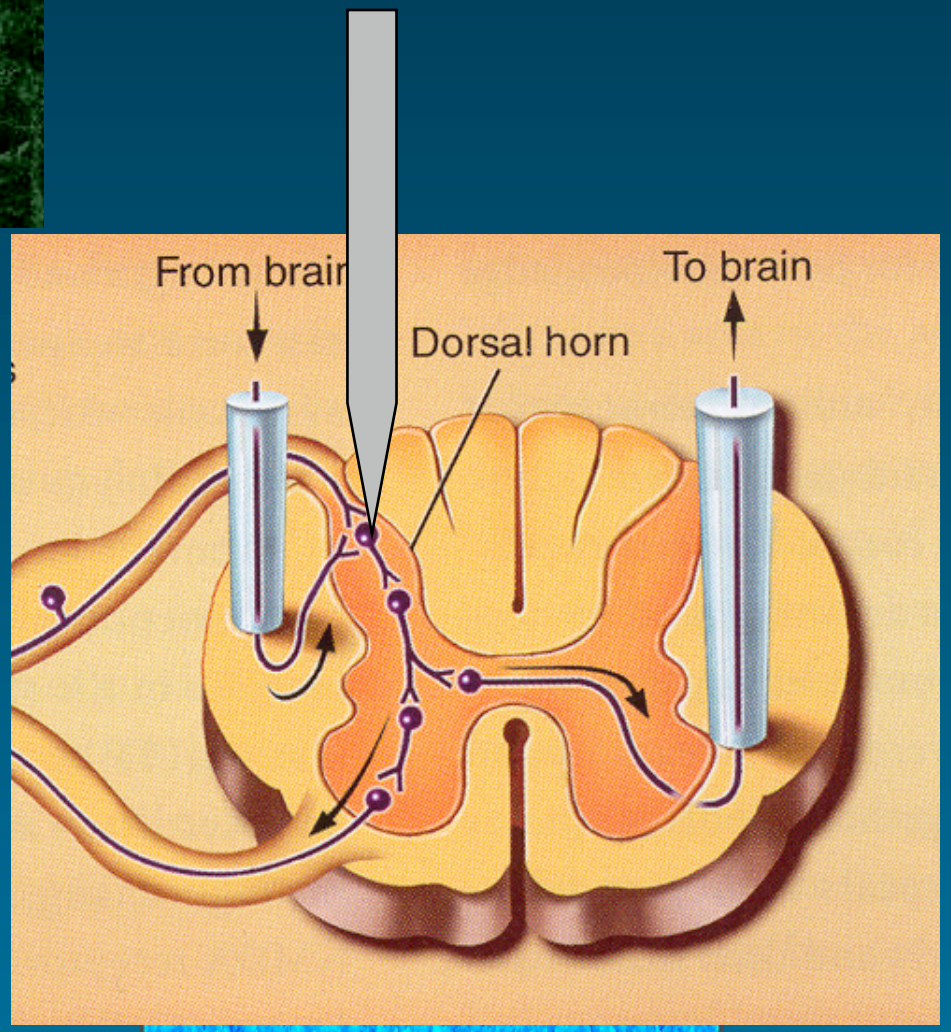
- Determine efficacy & safety of drug in a disease state
- Goals: Establish clinical indication in a specified patient population and Regulatory approval

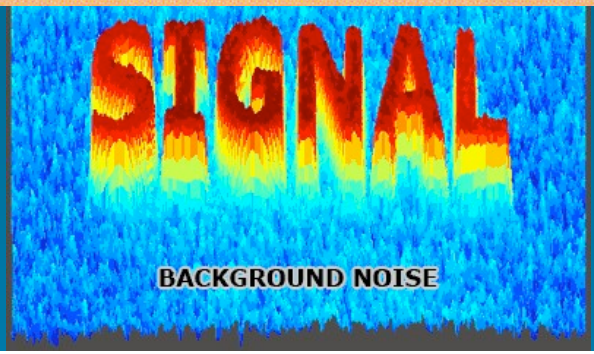
Assay sensitivity and Clinical trials
Balancing sensitivity with ….



Analogous to Enhancing Signal-Noise ratio

- Decreasing the noise
  - Better grounding of equipment, animal, etc.
  - Filters to reduce noice
- Improving the signal
  - Better electrodes
  - Get close to the cell





Improving Assay Sensitivity

- Design

(methods/outcome measures)

- Accomplice

(Patient / Subject)

- Disease

(Clinical model)

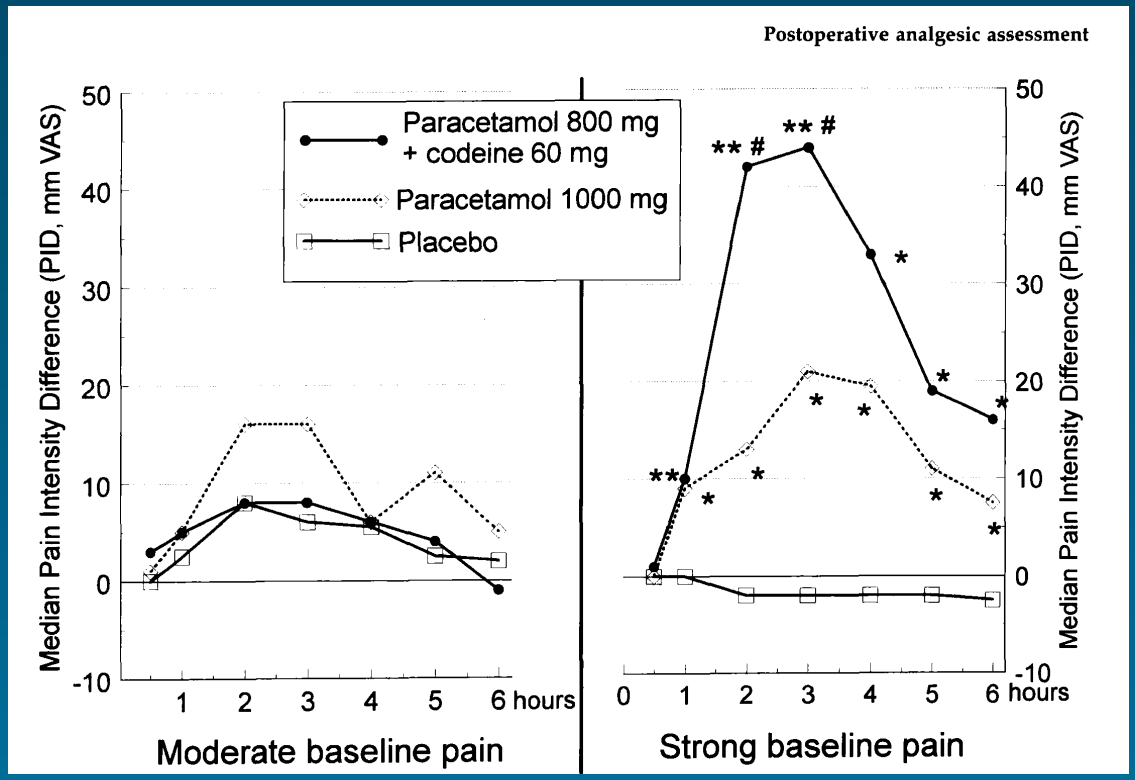
- Investigator

Optimizing Study Design

- Reducing Placebo response
  - Trial duration- short (Phase 2) vs longer (Phase 3)
  - Cross-over (Phase 2) vs parallel design (Phase 3)
  - Training of patients- improve reliability & decrease intra and inter-subject variability, manage expectations
- Dosing paradigm
  - flexible
- Outcome measures
  - Composite measures (pain intensity-relief-activity)?
  - Larger area under the curve (last 4 weeks vs 1 wk)
  - Biomarkers (Imaging for POC studies?)

Optimizing Study Population

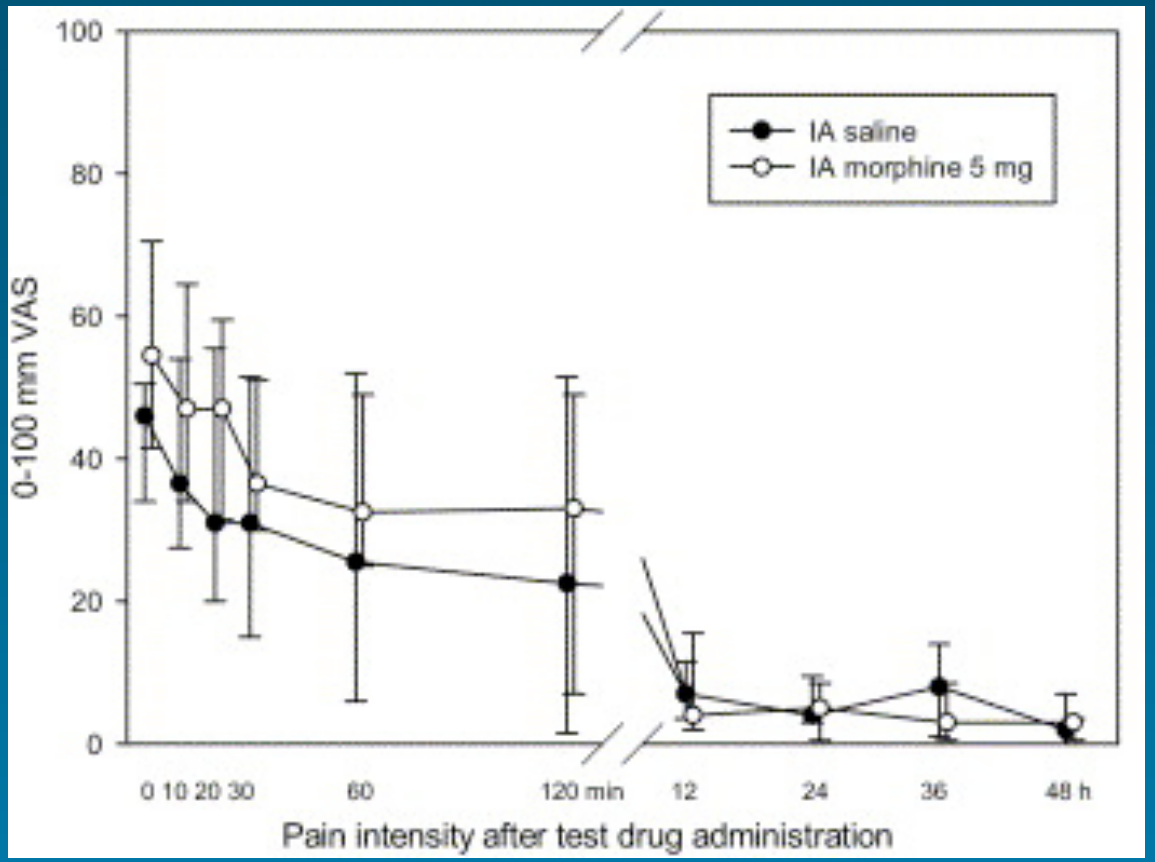
- Baseline pain severity and duration
- Compliant, skilled pain reporters (POC studies)
- Pain variability index
- Recruitment source
- Psychopathology
- Geographical/ cultural differences



Bjune et al. Act Anaesthesiol Scand 1998: 40:399

Baseline Pain and Assay Sensitivity

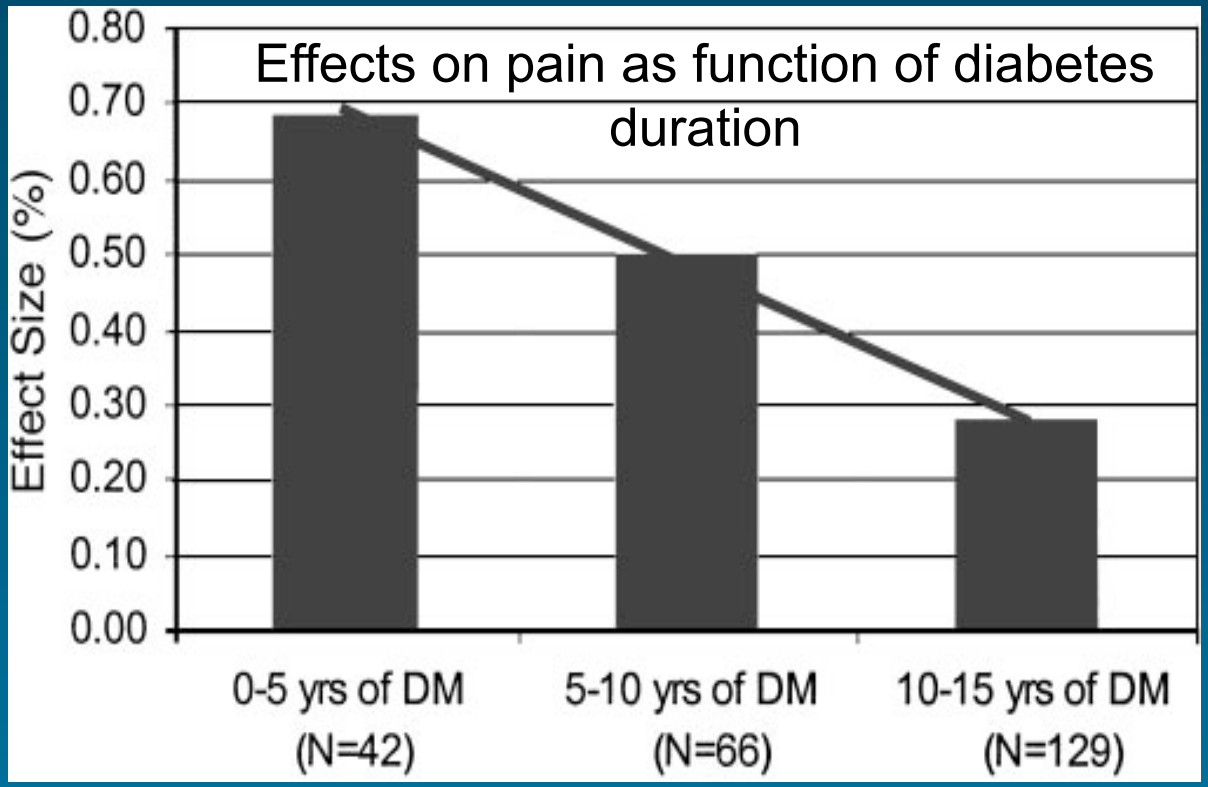
- No effect of intra-articular morphine in patients with moderate to severe pain



Solheim N et al.
Reg Anesth Pain Med
2006: 31:496

The Optimal Disease Population

- PHN vs PDN vs mixed
- Mechanistically homogenous group - phenotyping
- Optimal time in the course of the disease (natural course of the disease)



Acetyl-carnitine and diabetic neuropathic pain

Sima et al, Diabetes Care 2005;28;89

Optimizing Investigator Factors

- Training and experience of staff
- Minimizing staff-patient interactions
- Appropriate blinding
- Minimizing financial incentives for rapid recruitment
  - "Is bigger better for depression trials?" Liu KS et al. 2007
    A significant treatment effect before about 100 patients per arm, additional patients did not maintain achieved level of significance, one +ve study turned –ve.

Enhancing Assay Sensitivity: Potential Benefits

- Phase 2: Early identification of a “potential” promising compound in small POC trials
- Phase 3: Substantial evidence of consistent efficacy of the drug in a disease state, Regulatory approval

Summary: Enhancing Assay sensitivity

- **D**esign, **A**ccomplice, **D**isease, and **I**nvestigator
- Study design- consistent with the nature of question being asked: POC vs Confirmatory study
- Consider the balance of pros and cons of the design relative to the goals of the study: Sensitivity vs Generalizability of study results to the broader population