# Proof of Concept (POC) studies for neuropathic pain

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# POC studies for Neuropathic Pain: Outline

- What is it? (definition)
- Why do it? (potential uses)
- How can the signal to noise ratio be improved?
- What lessons can be learnt from Trial Designs of past neuropathic pain studies?
- Is there an Optimal Strategy?

# POC studies: definition

- The Concept: Engaging a particular target results in a meaningful change in a clinical end point thus identifying a new avenue to treat a condition/ disease in patients
- Strategy: Relatively small phase II clinical trial to confirm preclinical data demonstrating a novel mechanism may be a viable treatment

Wong DF et al. Neuropsychopharmacol Reviews 2008

# Goal of POC studies

- Testing New Molecular Entities
- Phase II: Early identification of a promising compound in small POC trials- helps make an early Go-No Go decision
- Estimate of treatment effect and its variance
- Not meant for regulatory approval

# POC studies in Neuropathic Pain
## Other Concepts that have been tested

- Is neuropathic pain sensitive to a certain drug class? e.g., opioids
- Are topical therapies effective in treating neuropathic pain? Test a new route of therapy/ site of action/mechanism
- Can novel formulations of an existing drug improve safety? Abuse deterrent opioids
- Is one class of drugs better than another for the treatment of neuropathic pain? Comparative studies

# An Optimal POC trial

- High assay sensitivity

"… the ability to distinguish an effective treatment from a less effective or ineffective treatment."

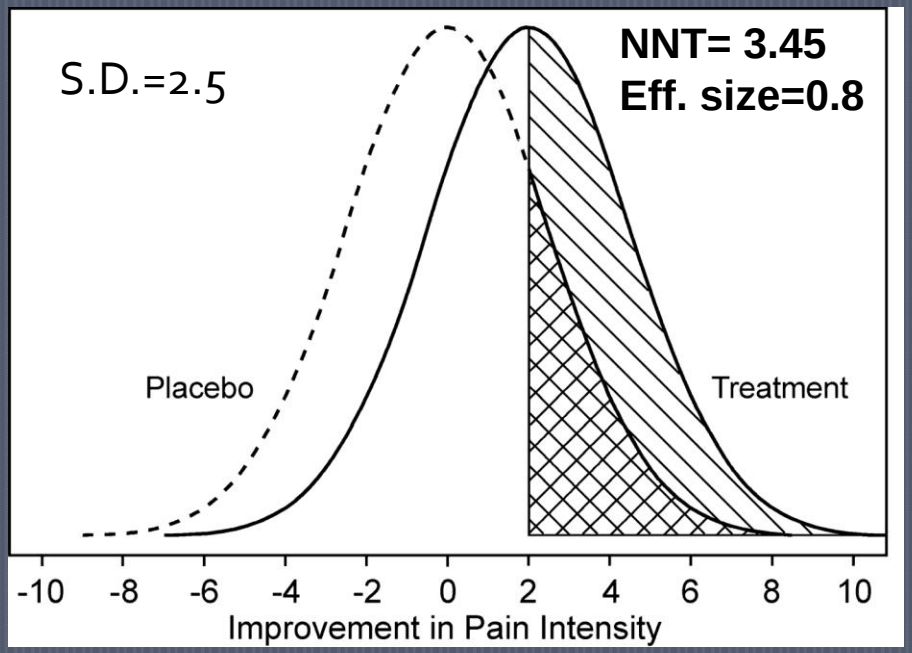
- Rapid enrollment
- Study duration relatively short
- Minimize exposure to placebo or ineffective therapy
- Moderate sample size
- Low drop out

www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125912.pdf

# Group differences:
## Minimizing placebo and maximizing drug effects

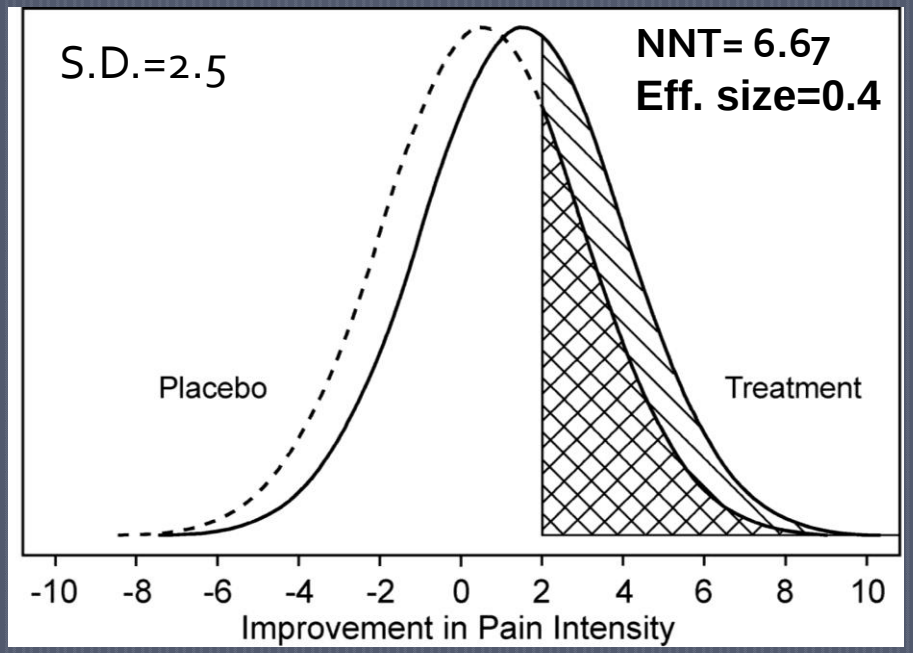
**Placebo**
Mean diff= 0
2 point diff= 21%

**Treatment**
Mean diff= 2
2 point diff= 50%




**Placebo**
Mean diff= 0.5
2 point diff= 27%

**Treatment**
Mean diff= 1.5
2 point diff= 42%




Dworkin et al. Pain 2009;146:238

# Enhancing Signal-Noise ratio in neuropathic pain

- Disease- Clinical model
- Design- Trial methods (parallel vs cross-over, enriched designs, fixed vs flexible dosing, rescue meds
- Subject: pain intensity min-max, duration, variability, training
- Outcome measures and Interpretation
- Investigator(s)- no of sites, training

# Disease: Clinical Model
# Neuropathic pain trials


Industry

- Gabapentin and pregabalin
  - PHN, diabetic neuropathy
- Duloxetine
  - Diabetic neuropathy
- Tapentadol
  - Diabetic neuropathy
- Topical NGX-4010
  - PHN, HIV neuropathy

- Nortriptyline + Gabapentin
  - PHN or diabetic neuropathy
- Morphine + Gabapentin
  - PHN or diabetic neuropathy
- Levorphanol
  - Peripheral or central neuropathic pain
- Nabilone vs dihydrocodeine
  - Neuropathic pain

Academia

# Lumping: Neuropathic Pain

## PRO

- Easier to recruit
- Study duration shorter
- Fewer sites needed- decreases site variability
- Greater generalizability
- Helps examine drugs in less common pain states

## CON

- Assumes common underlying mechanisms
- More variability in data?
- May result in false negative if drug effective in some, but not all disease states
- May not be helpful in the regulatory process

Rowbotham. Neurology 2005;65 suppl 4:S66

# Splitting: Specific neuropathic pain state

**PRO**

- Homogenous group
- Less variability
- Easier to analyze data from multiple studies (meta-analysis)
- Establishes disease to study for subsequent phase 2 and 3 studies

**CON**

- Limited generalizability
  Does not predict if drug likely to be effective in other disease states
- Slower recruitment
- Multiple sites needed
- Less common diseases may not be studied

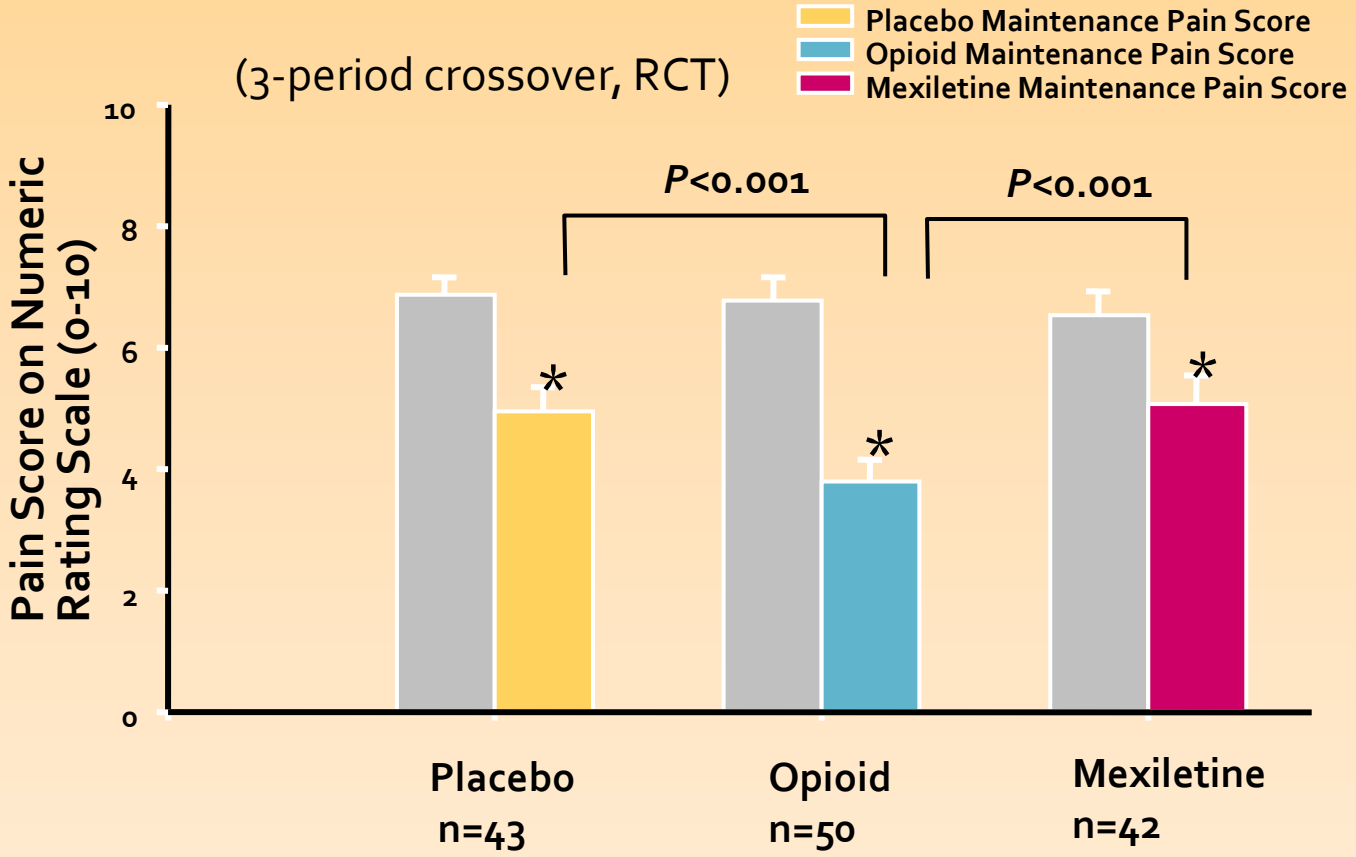
# Study Designs

- Parallel vs Crossover
- Enriched enrollment design
  - Time to withdrawal design
- Mechanism-based clinical studies (Wallace MS 2002 J Pain)
- Split-trial strategy- pooled data from few centers with extensive testing

Rowbotham M Neurology 2005;65:S67

# Is neuropathic pain resistant to opioids?

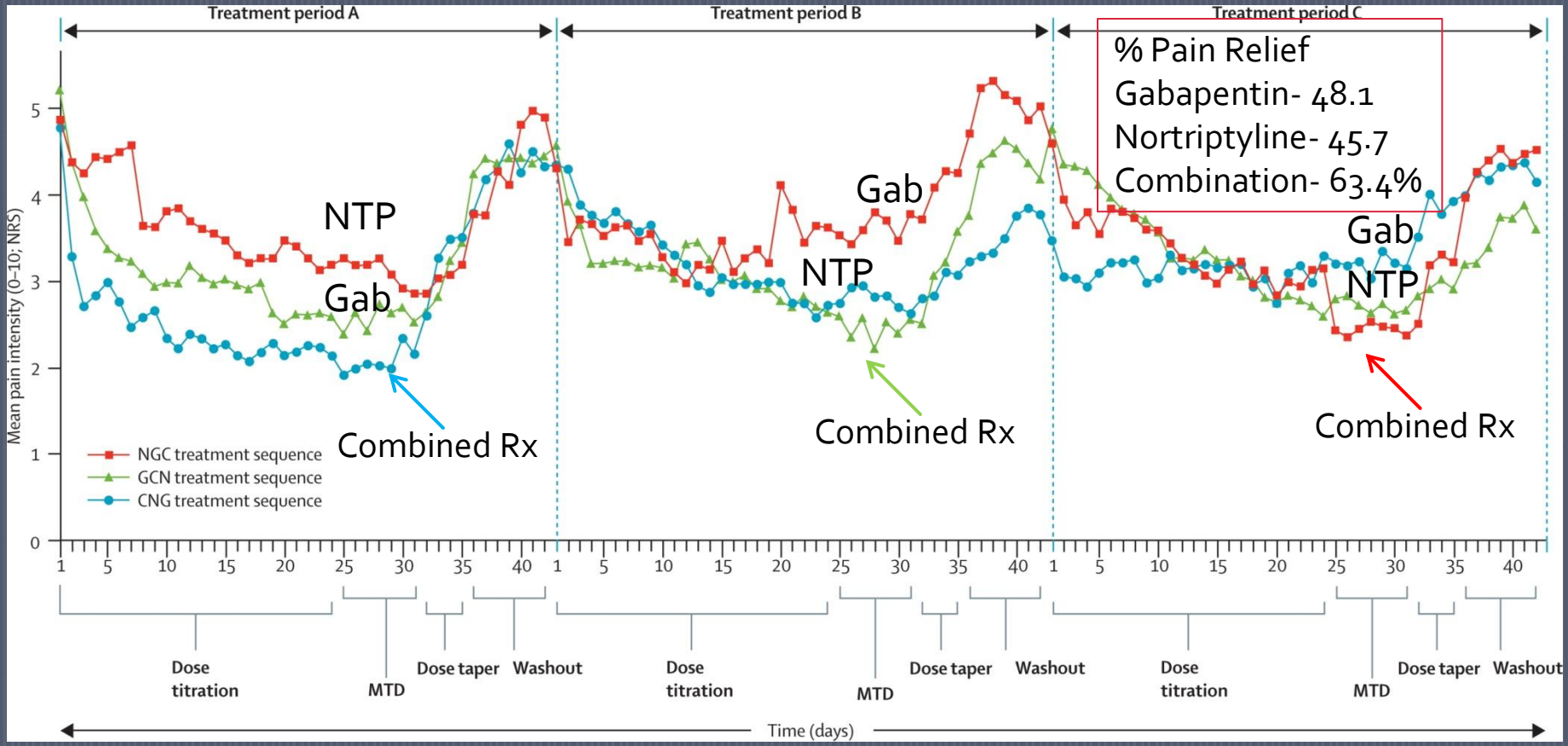
## Opioid vs Sodium channel blockers on postamputation pain- double-blind cross-over studies




Wu et al. *Anesthesiology* 2008;109:289

# Combination therapy enhances efficacy
# Nortriptyline and gabapentin cross-over RCT

40 DPN, 15 PHN subjects- 3 different sequences to control for order effects



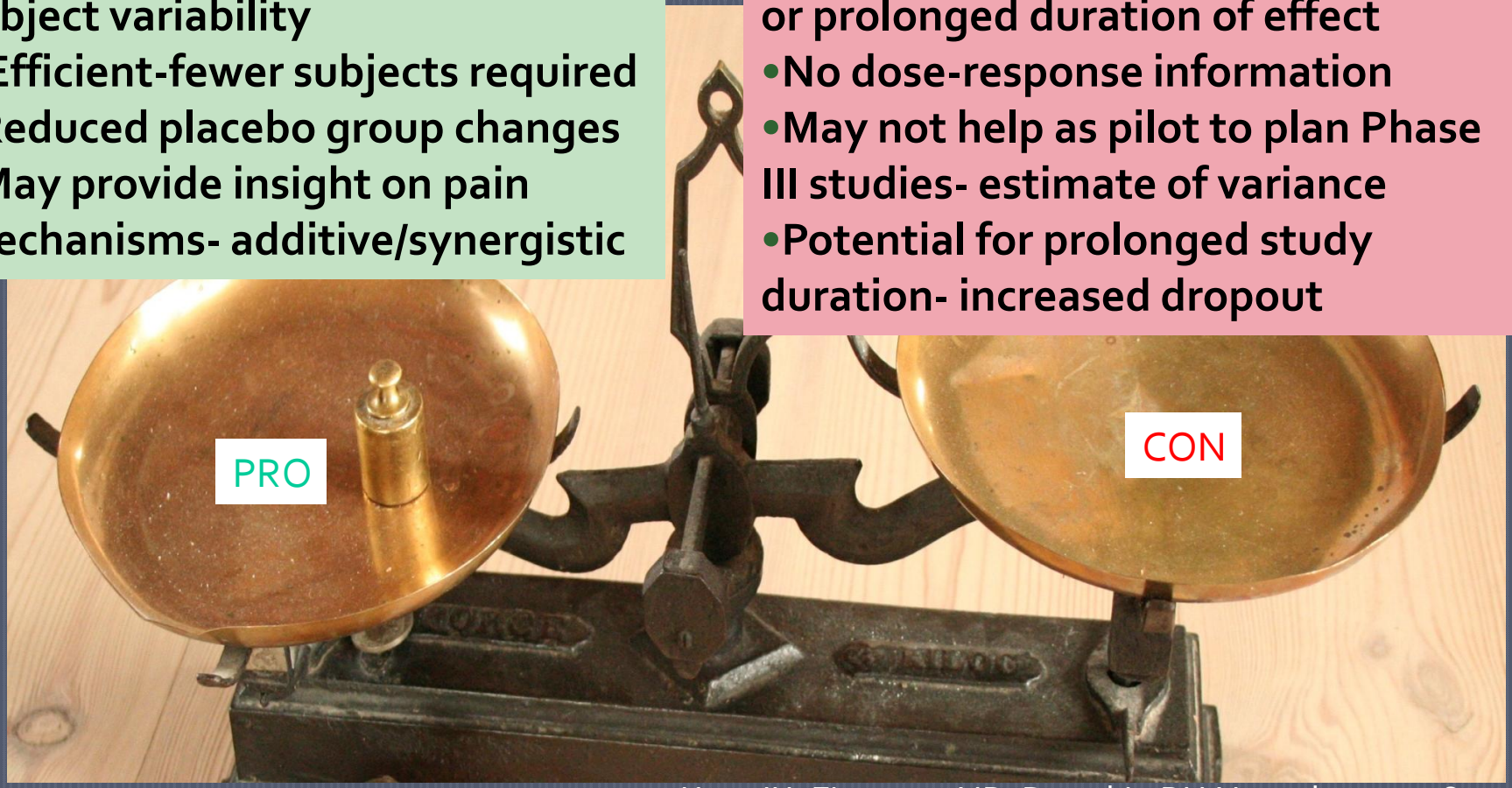

Within subject comparison
Patient numbers relatively small

Gilron I et al. Lancet. 2009;374:1252

# Cross-over trials: Pros and Cons
# Head to head comparisons

- Minimizes effects of inter-subject variability
- Efficient-fewer subjects required
- Reduced placebo group changes
- May provide insight on pain mechanisms- additive/synergistic

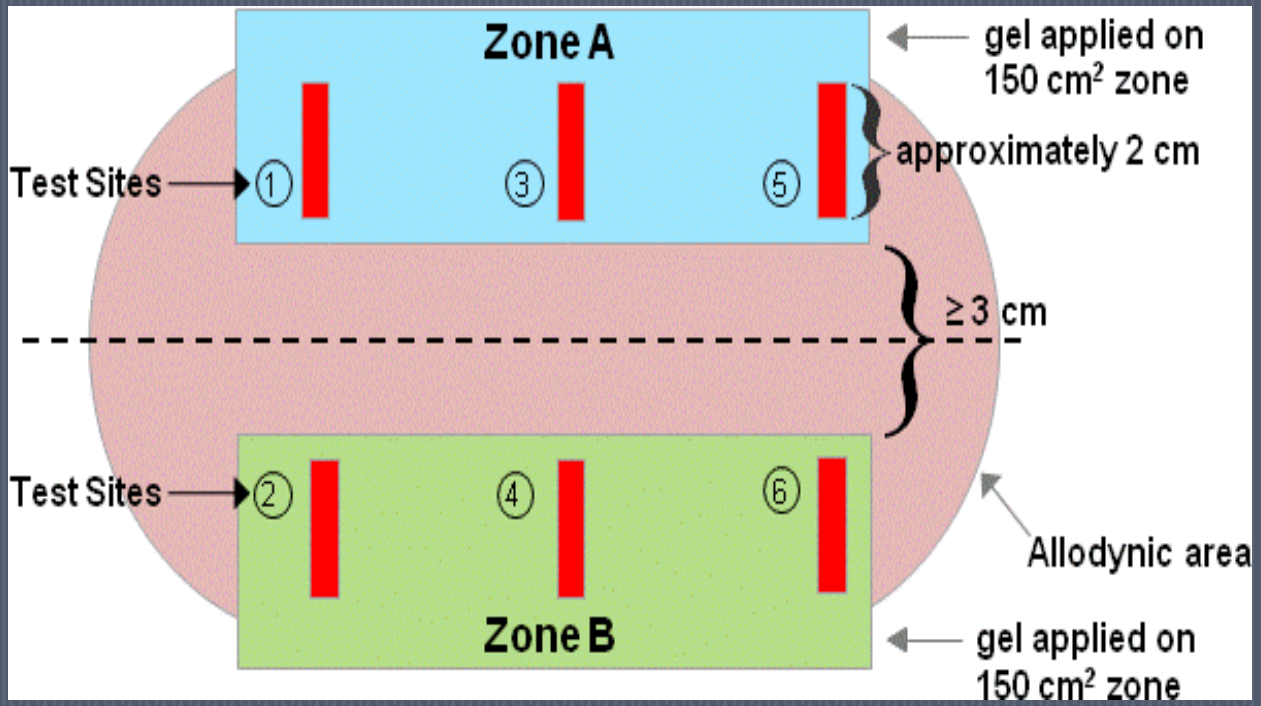
- Carry over effects from slow offset or prolonged duration of effect
- No dose-response information
- May not help as pilot to plan Phase III studies- estimate of variance
- Potential for prolonged study duration- increased dropout

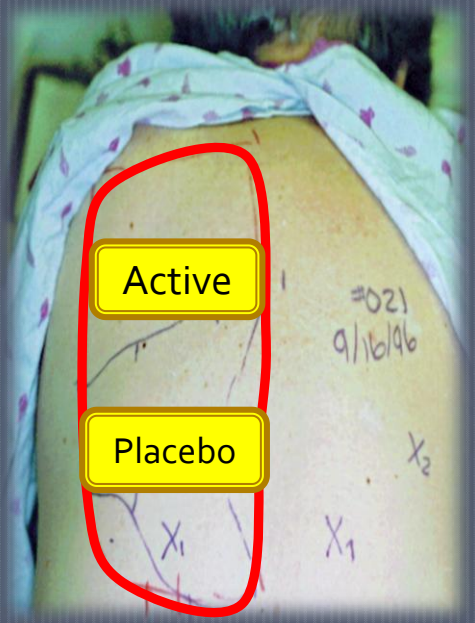



Katz JK, Finnerup NB, Dworkin RH Neurology 2008;70:263
Polydefkis M, Raja SN Neurology 2008;70:250

# POC study for topical agents Within subject comparisons

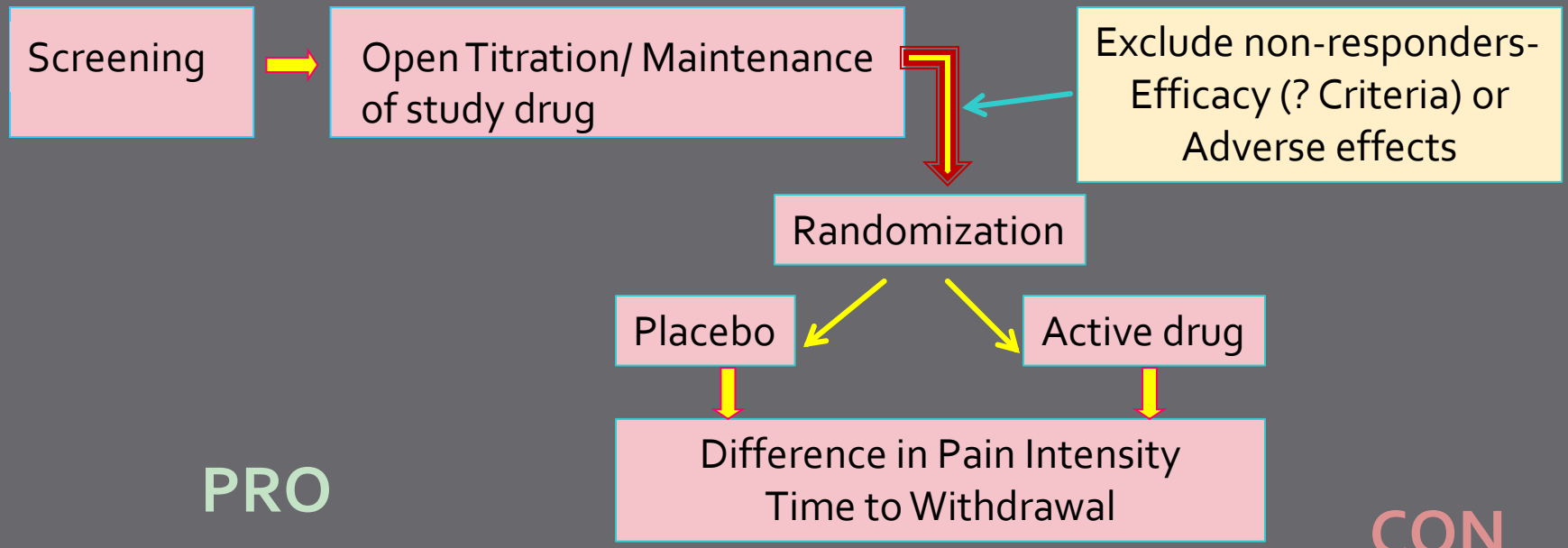
- Within subject comparison of vehicle vs active drug on allodynia




Courtesy J Campbell, Arcion Therap.

# Enriched Enrollment Randomized Withdrawal Design



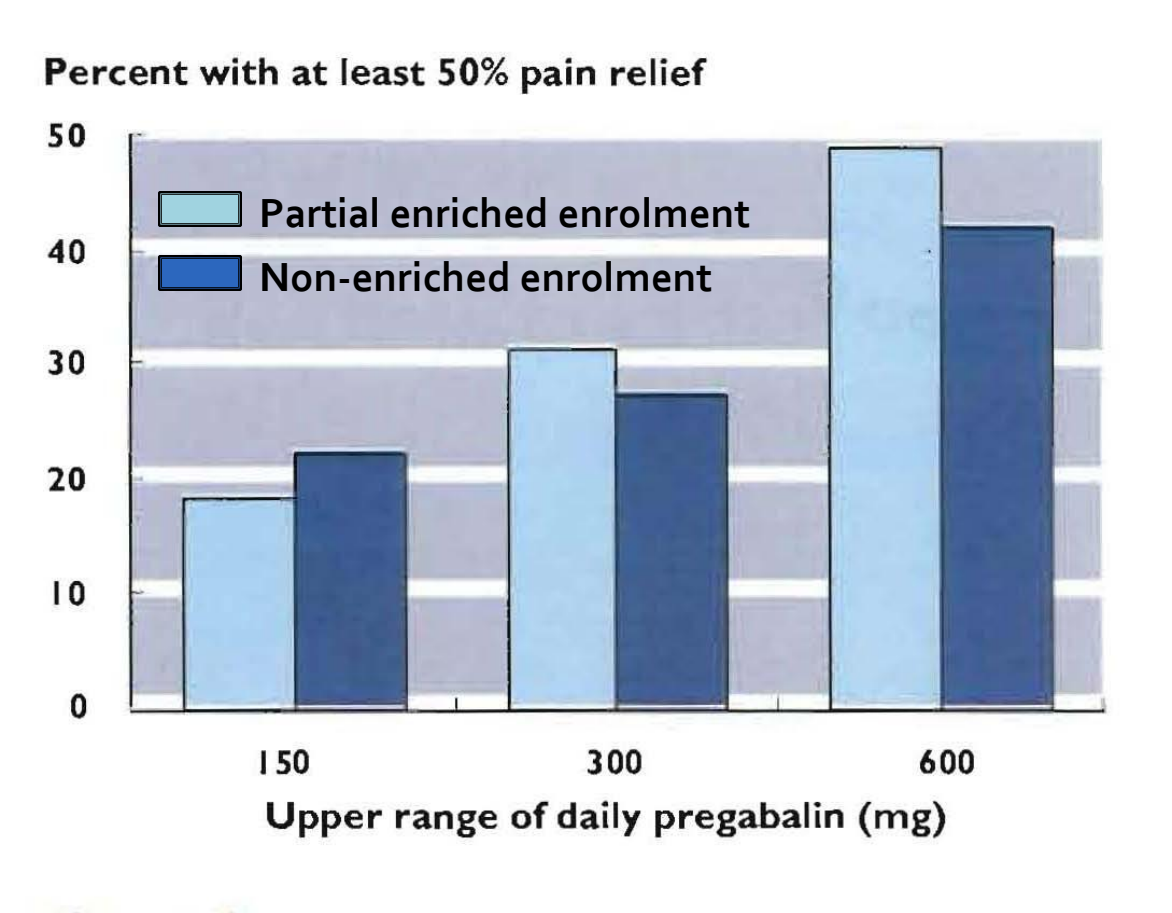

## PRO

- Greater drug-placebo difference
- Lower variability and increased effect size
- Time to efficacy failure more sensitive end point

## CON

- Generalizability to population
- Potential for carry-over effects from initial drug exposure
- Unblinding of the placebo gp

# Systematic review of Enriched Enrollment Trials of pregabalin and gabapentin in neuropathic pain

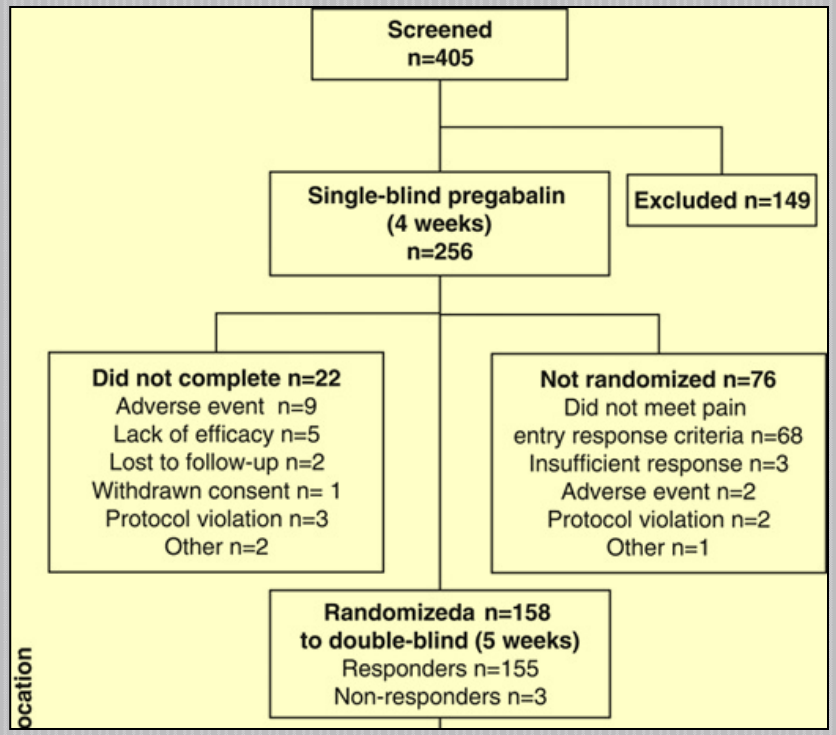


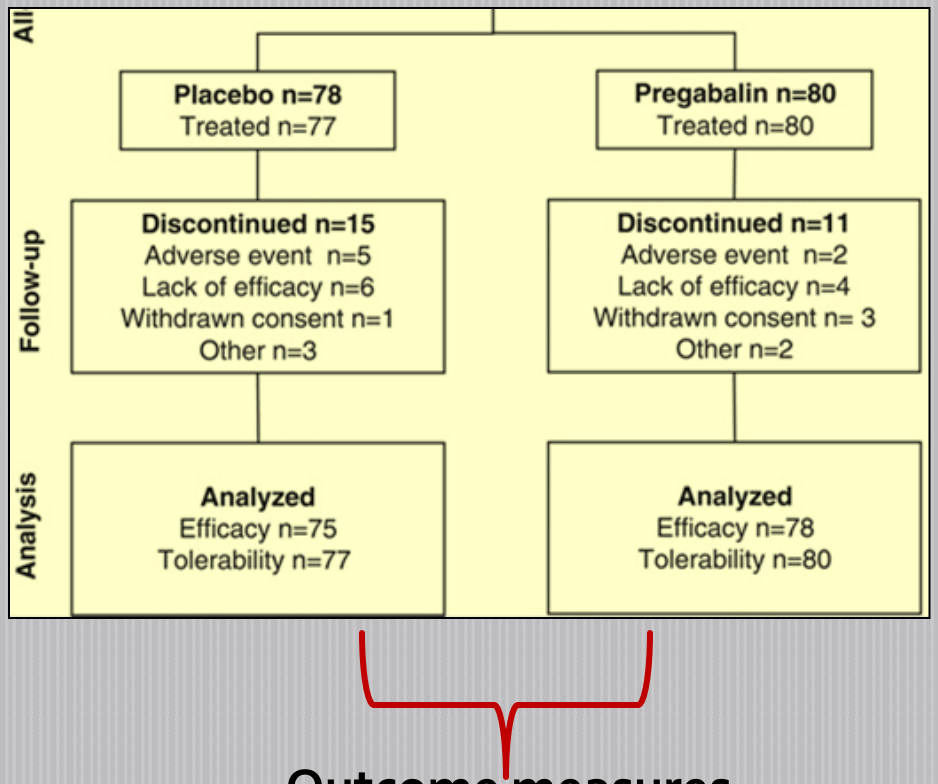

7 trials with PEE
14 NEE trials

Straube et al. 2008
Br J Clin Pharmacol.
2008;66:266

- Estimates of efficacy unchanged
- Inadequate enrichment or enhancement of treatment effect minimal

# Pregabalin for Peripheral Neuropathic Pain: A Multicenter, EERW Placebo-controlled Trial



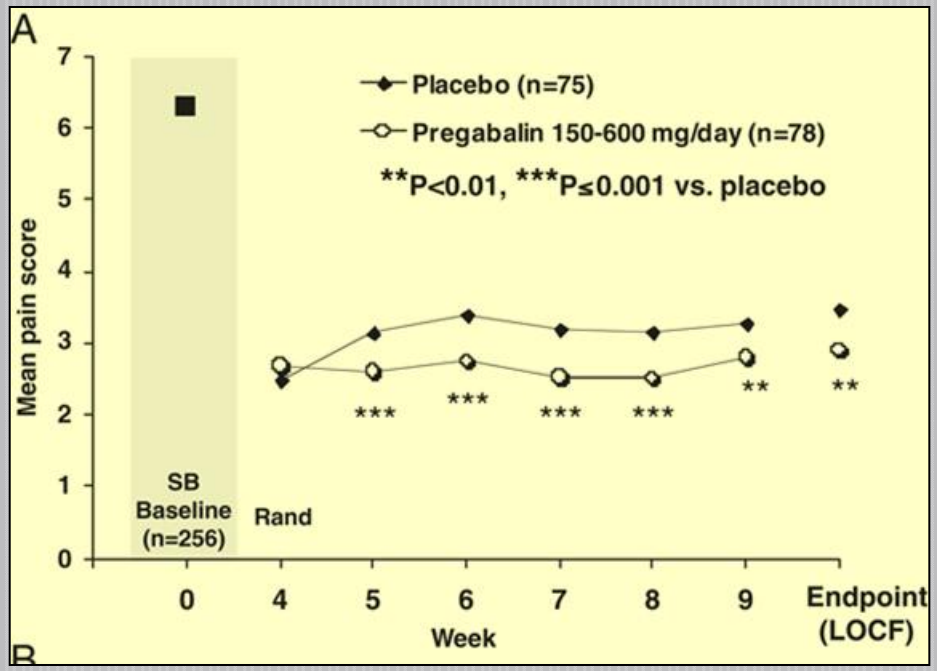

DPN, PHN, other diagnosis

≥ 30% reduction in pain score at week 4

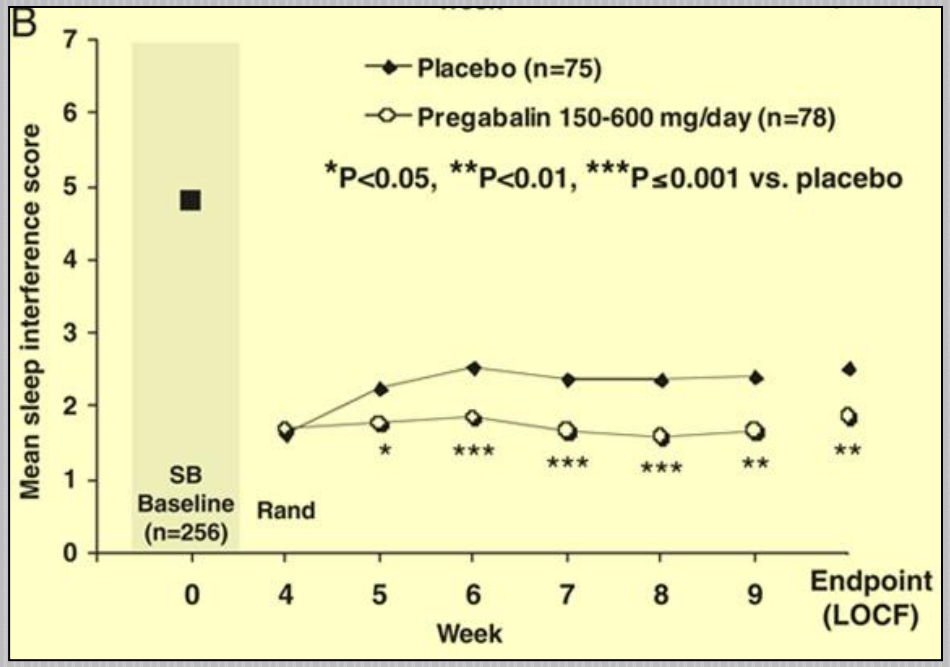
40% pt not randomized

Gilron I et al.
Clin J Pain. 2011;27:185

# Pregabalin for Peripheral Neuropathic Pain: A Multicenter, EERW Placebo-controlled Trial



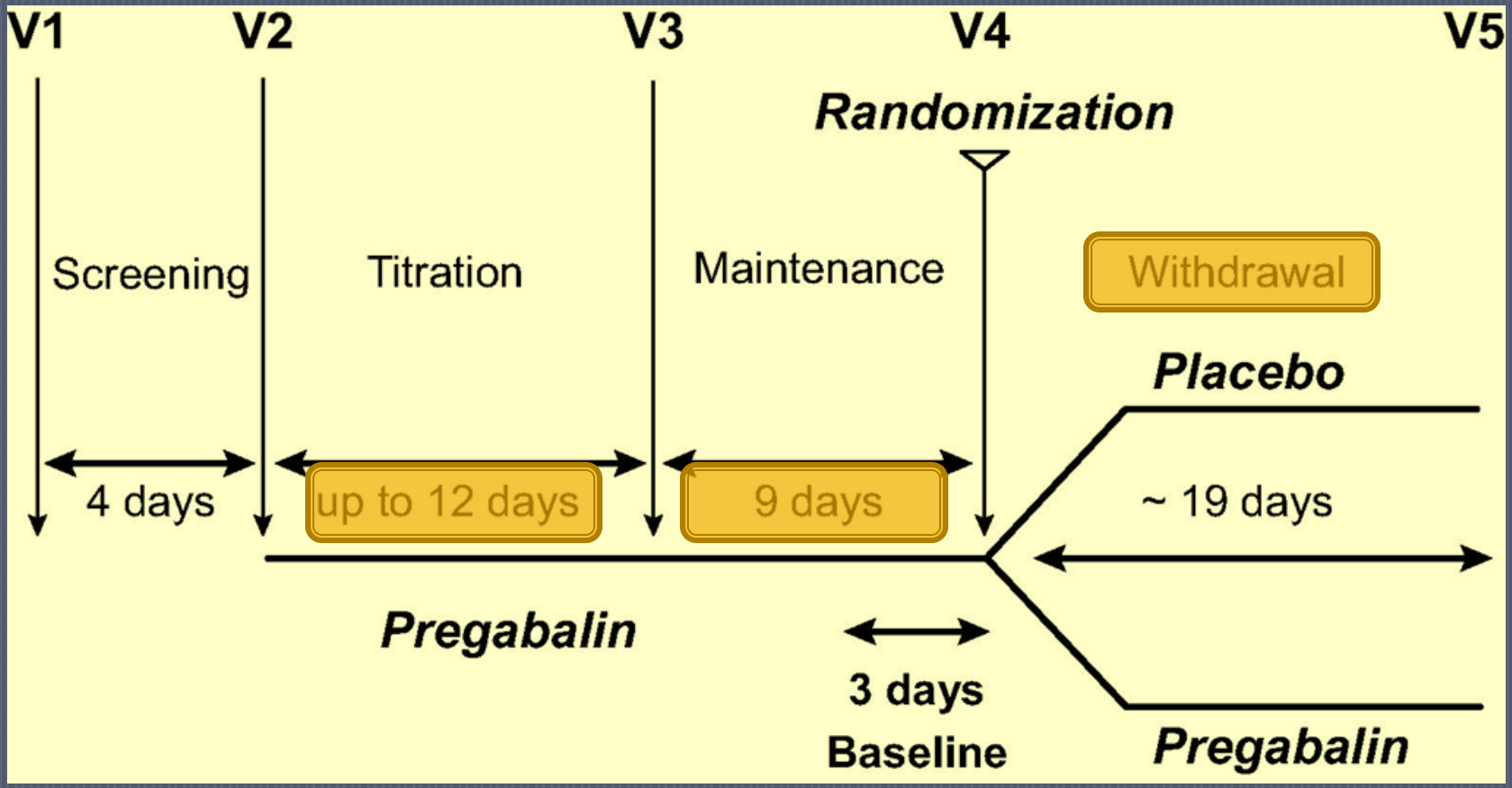

PAIN




SLEEP

Gilron I et al.
Clin J Pain. 2011;27:185

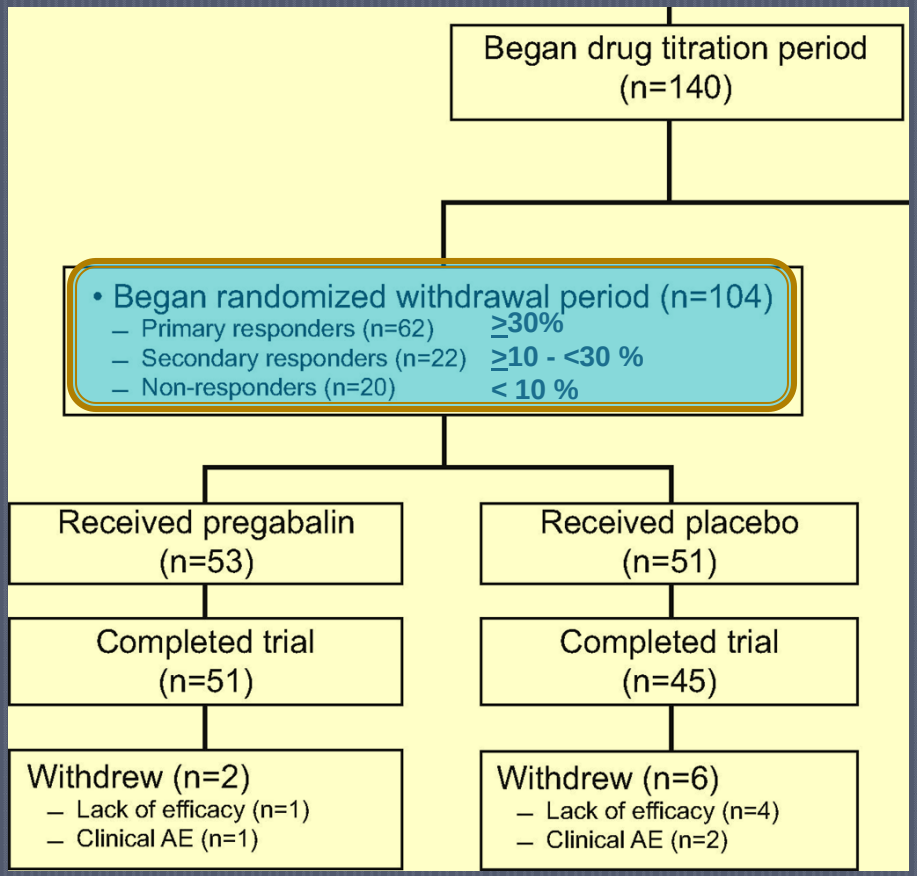
# POC in neuropathic pain: Enriched enrollment randomized withdrawal design

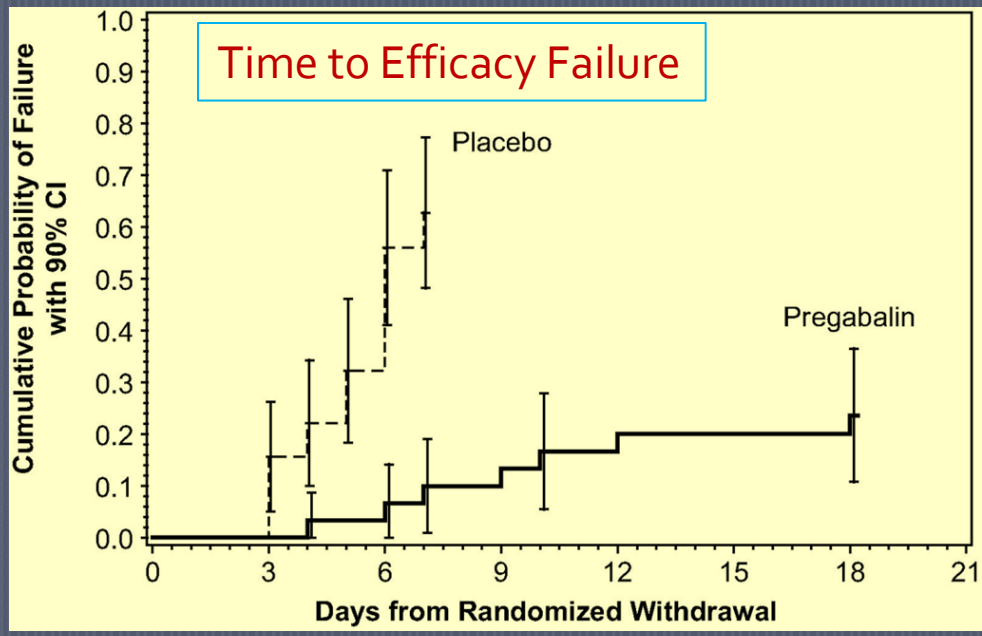



Subjects: DPN, PHN, small fiber neuropathy, idiopathic sensory neuropathy

Hewitt DJ et al. Pain 2011;152:414

# Enriched enrollment randomized withdrawal design for POC: Pregabalin for neuropathic pain




- Efficacy failure >50% by day 6 for placebo gp.
- <30% for pregabalin end of Rx
- Effect size > for efficacy failure vs change in pain intensity
- Largest effect size in responders-open phase

Hewitt DJ et al. Pain 2011;152:414

# Enriched Designs with Randomized Withdrawal: Pros and cons

PRO

- Increased assay sensitivity
- Short duration trial
- Drop outs less of an issue as that is the end point during blinded phase

CON

- Assumes rapid titratability and onset of drug effect

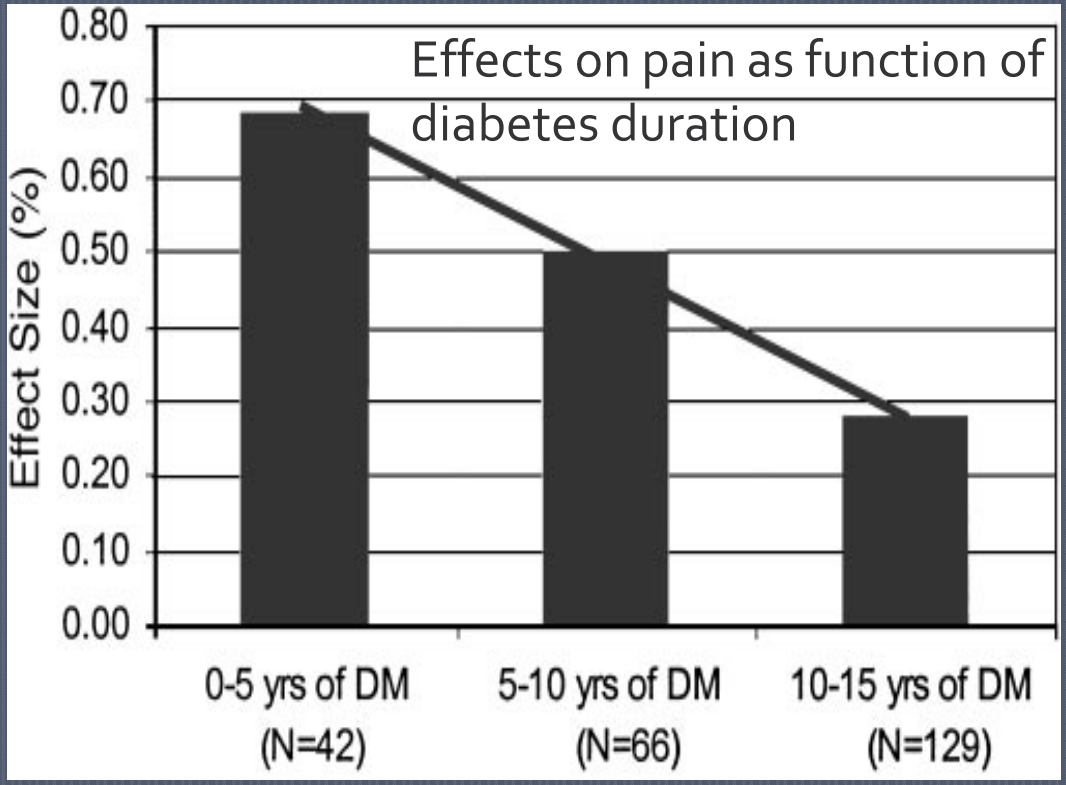
# Optimizing Study Population
## IMMPACT recommendations

- Baseline pain severity (≥4 and ≤9) and duration (≥6 m)
- Baseline diary compliance ≥6/7 per week
- Trained subjects: skilled pain reporters, manage expectation bias
- Pain variability- lack of?
- Baseline pain consistency?
- Discarding high placebo responders?
- Psychopathology
- Geographical/ cultural differences

Bjune et al. Act Anaesthesiol Scand 1998: 40:399
Dworkin et al. IMMPACT on Assay sensitivity, 2011

# The Optimal Disease Population

- Optimal time in the course of the disease (natural course of the disease)

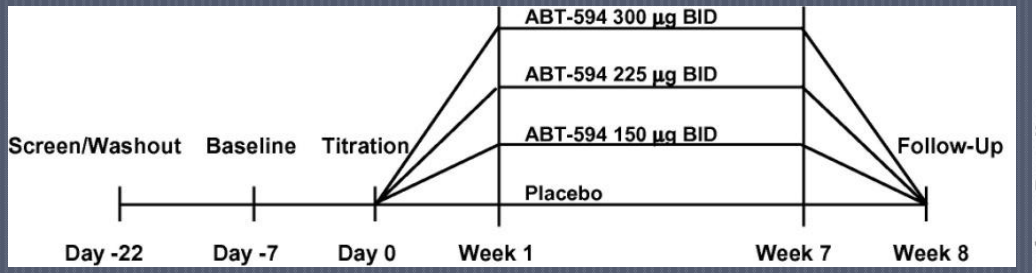


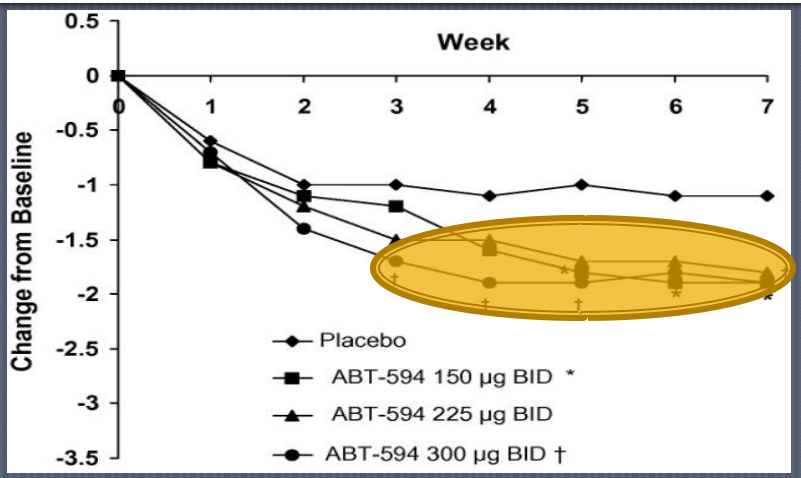

Acetyl-carnitine and diabetic neuropathic pain

Sima et al, Diabetes Care 2005;28;89

# POC: The balance between efficacy and adverse effects

# ABT-594 in diabetic neuropathic pain
## (Neuronal nicotinic acetylcholine receptor agonist)




| | Placebo | ABT-150 x 2 | ABT-225 x 2 | ABT-300 x2 |
|---|---|---|---|---|
| Change in Pain Intensity | - 1.1 | -1.9 * | - 1.9 * | - 2.0 * |
| Discontinuation rate | **22 %** | **38 %** | **57 %** | **75 %** |
| Adverse Events | **9 %** | **28 %** | **46 %** | **66 %** |

Nausea, dizziness, vomiting, asthenia

Rowbotham et al. Pain 2009; 146:245

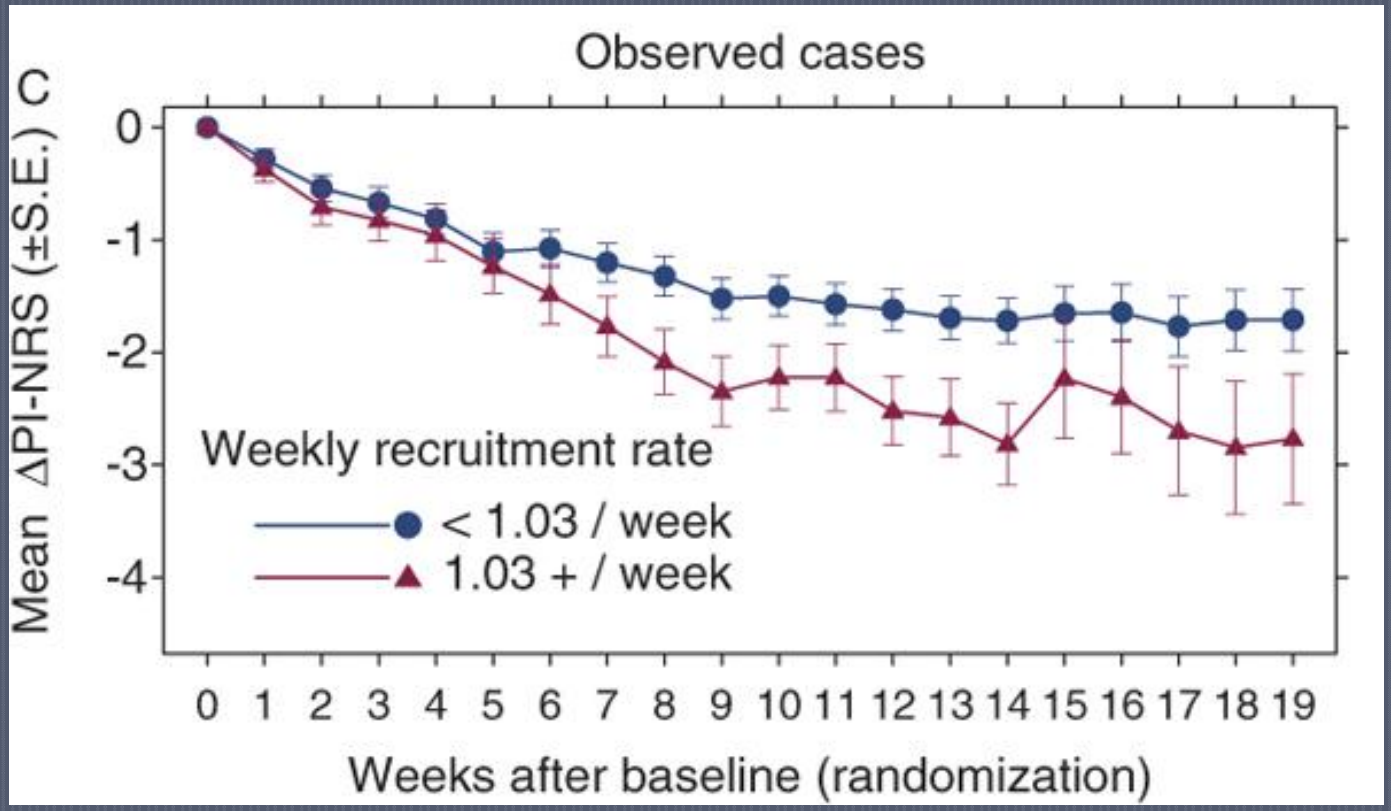
# POC: Optimizing Investigator and Site Factors

- Minimize number of sites: Infrastructure, Variable training and experience of staff
- Minimize staff-patient interactions
- Appropriate blinding of investigative team
- 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

Dworkin et al. IMMPACT on Assay Sensitivity, 2011

# POC: Site recruitment rate and placebo Pooled data from 3 lamotrigine trials for NP

- Site recruitment rate- an independent predictor of placebo response




Irizarry et al. Clin J Pain 2009;25:469

# Summary: Optimizing POC study design

- Study design- consistent with the aim of the study
- Factors to consider: Disease, Design, Subject, Outcome measures, and Investigator

# Enhancing signal to noise

- Decrease placebo response?
  - Enroll patients with greater baseline pain severity
  - Use Flexible vs Fixed dose designs
  - Minimize number of treatment groups
  - Strategies to decrease staff and pt expectations
- Crossover or enriched design?
- Short term trials, sample size?
- Active comparators?

# The Optimal Strategy

## No single ideal trial method