Accelerating the Development of Enhanced Pain Treatments
March 25, 2011 - Bermuda

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Proof-of-concept trials

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How can POC trials make us more "ADEPT"?

Is there a problem?

- pharmaceutical industry in general:
> 60% of new molecular entities *fail in phase 2* *(Kola, '04)*

- NME approvals by US FDA since 2005:
only ONE out of ~100 was for pain treatment *(Dworkin, '11)*

Why?

- limited predictive value of preclinical studies?
- limitations in early POC trial design?
- limitations in overall clinical development strategies?

Woolf, 2010

Defining the target population for POC trials

"Disease/tissue"- based

- e.g. arthritis, sometimes homogeneous mechanism/Tx response?

- association between pain condition and targetable group of clinic
may facilitate trial recruitment & future clinical Rx implementation

"Mechanism/phenomenon"-based

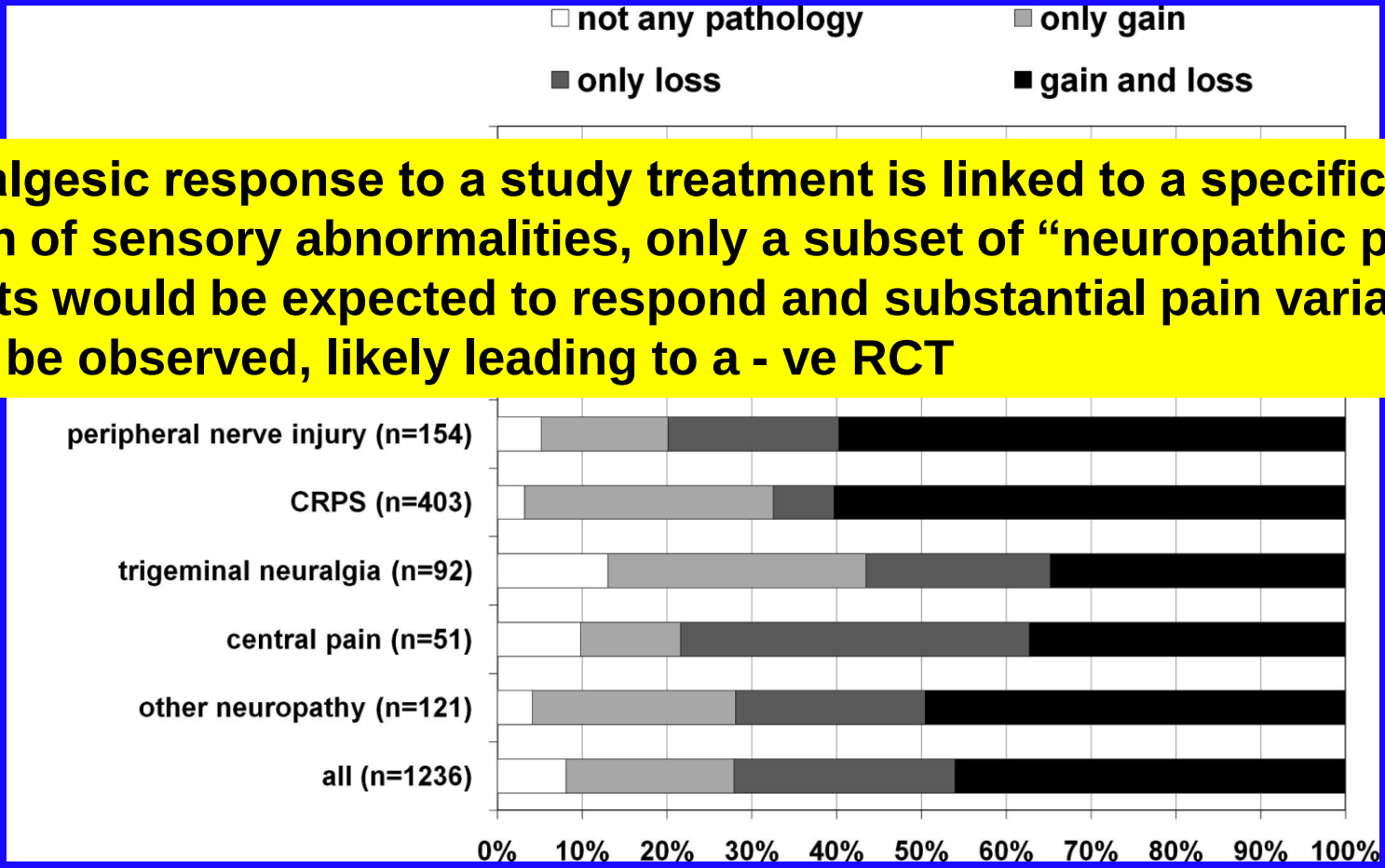
- e.g. tactile allodynia, mechanical hyperalgesia or pain on movem

- if study treatment can be matched to a discrete mechanism, Tx e
size and generalizability could be optimal

- more difficult to target for trial recruitment & future practice

Max, 1990; Woolf & Max, 2001

Problems with a disease-specific target population



- **If analgesic response to a study treatment is linked to a specific pattern of sensory abnormalities, only a subset of "neuropathic pain" patients would be expected to respond and substantial pain variance would be observed, likely leading to a - ve RCT**

Fig. 4. Sensory findings (gain or loss) according to the neurological syndrome. For each patient (n = 1236) QST data of the painful area were scored. For each healthy subject (n = 180) all 6 test areas were scored, yielding 1080 areas. "Without any pathology": none of the QST parameters was outside the 95% CI and there was no relative abnormality, "Only loss": at least 1 abnormally increased thermal or mechanical detection threshold, but neither thermal nor mechanical hyperalgesia. "Only gain": at least 1 abnormally decreased thermal or mechanical pain threshold, increased mechanical pain sensitivity, decreased pressure pain threshold or DMA, but neither thermal nor tactile hypoesthesia. "Gain and loss": at least 1 +ve sign combined with at least 1 -ve sign.

Maier et. al., PAIN 2010

What about a "mechanism"-based target population?

• Wallace *et. al.*, '02: **"neuropathic pain with allodynia"**

- Na^+ blockade with 4030W92 had no effect on **spontaneous** pain (1^0)
but did reduce allodynia severity (day 1) & area (day 7)

• Nurmikko *et. al., '07:* **"neuropathic pain & allodynia"**

- sativex reduced "global neuropathic pain" (1^0) and also allodynia

• AstraZeneca: **"neuropathic pain & mech hypersens'y"**

- AZD2066 (NCT00939094-completed), 1^0 outcome: "pain intensity"

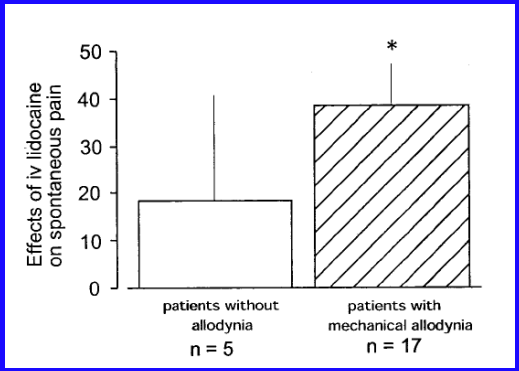
Problems:

1) Is the study Tx matched to the target mechanism?

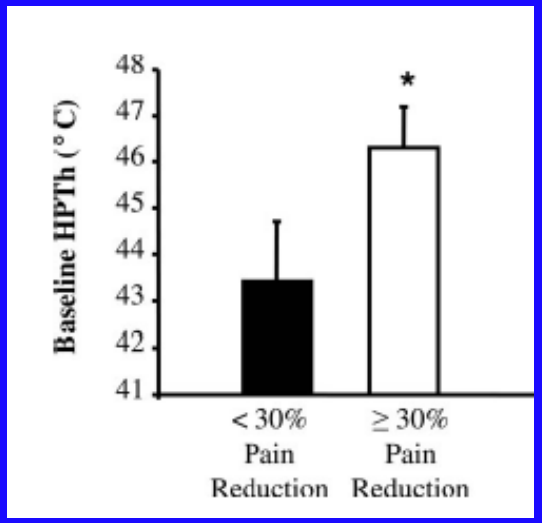
2) Is the primary outcome matched to the target mechanism?

mechanism vs. predictor of response

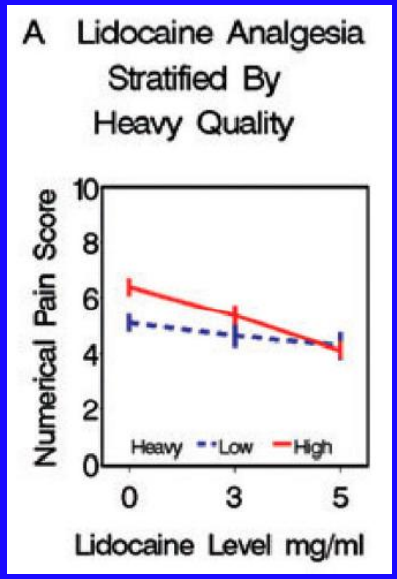
Is there a difference?



Attal et. al., 2004



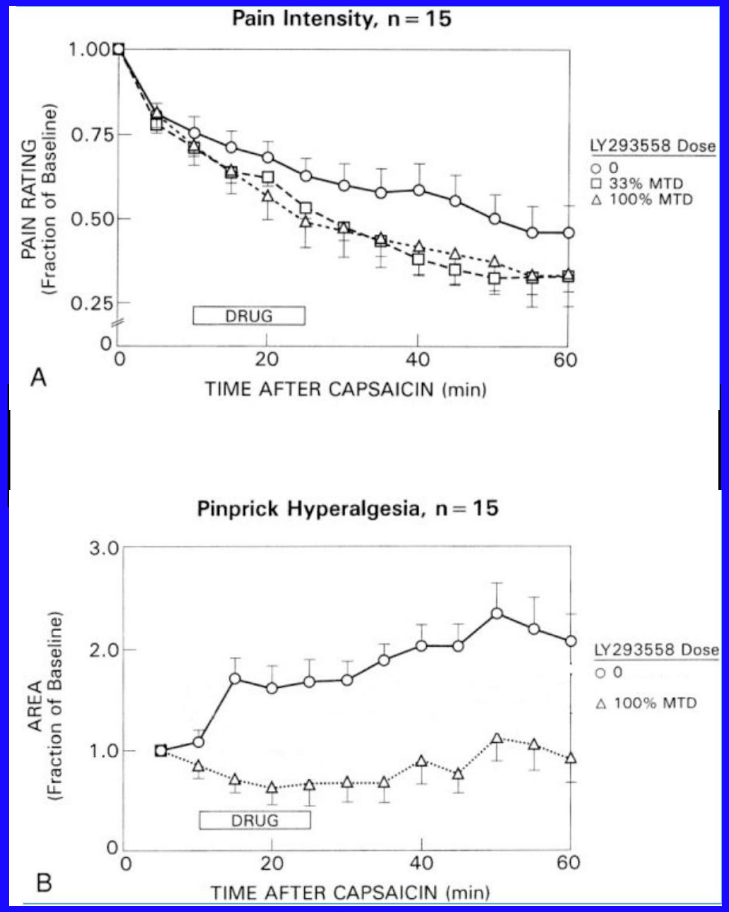
Edwards et. al., 2006



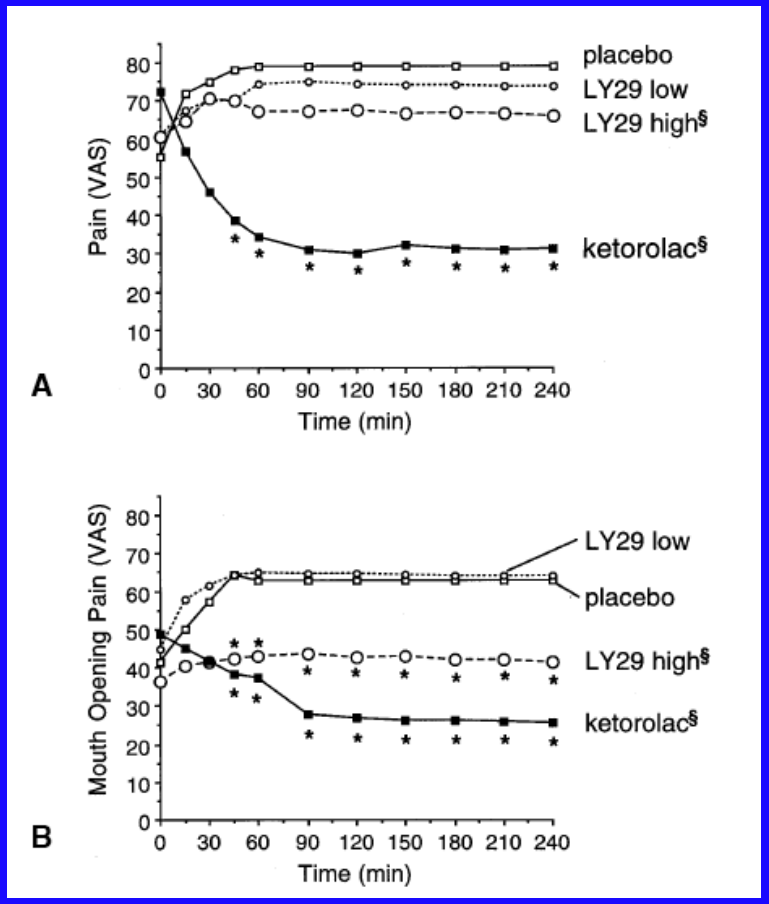
Carroll et. al., 2010

Mechanism vs. predictor of response

spontaneous vs. evoked pain



Sang et. al., 1998



Gilron et. al., 2000

"Mechanism"-based POC design: A proposal

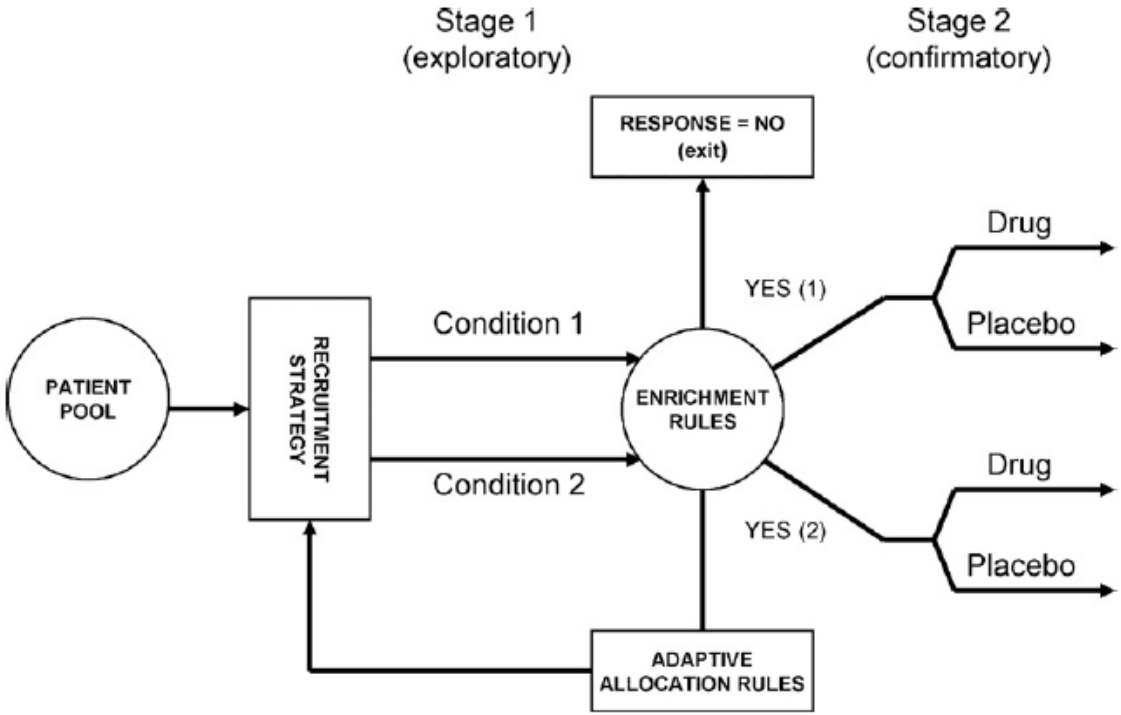


Fig. 1. Schematic for a 2-variable input enriched adaptive reallocation model. Patients selected based on meeting one of two non-overlapping conditions or baseline characteristics (condition 1 or 2) receive a drug trial in Stage 1 according to a defined algorithm such as individual dose titration to tolerance or effect. Patients achieving predefined responder criteria enter a randomized withdrawal trial in Stage 2 (stratified by condition). The recruitment strategy is adaptively modified based on the differential proportion of responders in the two input conditions. Recruitment into one or both condition groups may cease based on futility rules. The primary analysis in Stage 2 contrasts all drug against all placebo.

Quessy, 2010

"Pain intensity" is inherently a composite measure

- Pain dimensions

- sensory-discriminative/emotional-affective descriptors, many distinctive qualities *(Melzack, '75; Gracely, '78; Galer & Jensen, '97)*

- temporal features: continuous, intermittent, lancinating, *(Bouhassira et. al., '04)*, diurnal variation *(Bellamy et. al., '91; Odrcich et. al., '06)*

- spontaneous vs. evoked *(Bennett, '01; Gilron et. al., '00, '05)*

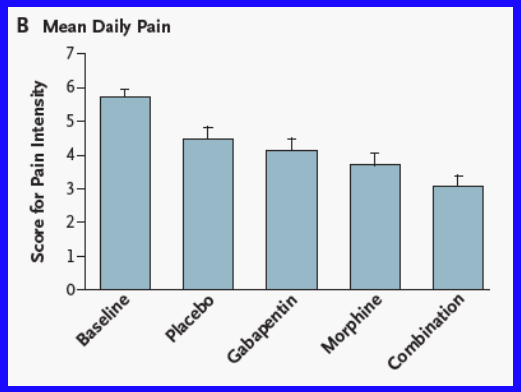
****Pattern and relative contribution of the above to individual symptom burden likely varies widely*

- Pain report

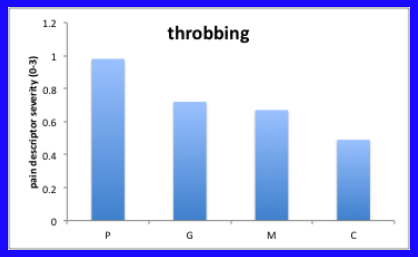
- **Lumping**: single rating of "average" pain over last 24h – subjects individualize their interpretation/report *(Williams et. al.*

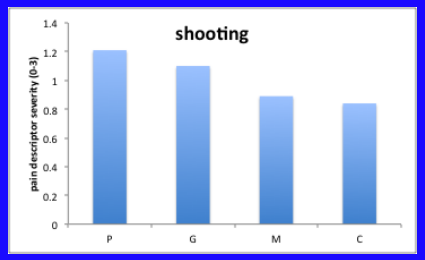
Deconstructing the analgesic response

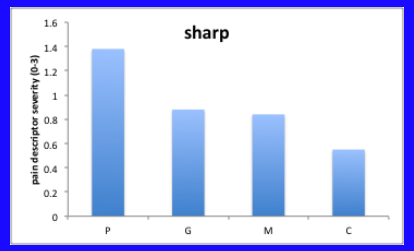
1^0 outcome:
0-10 NRS intensity

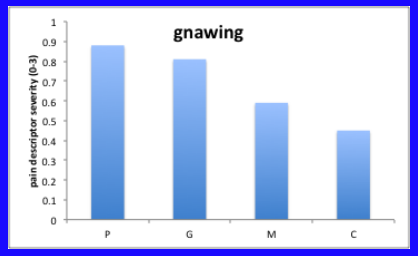


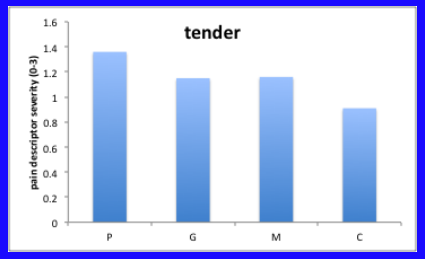
Gilron et. al., 2005

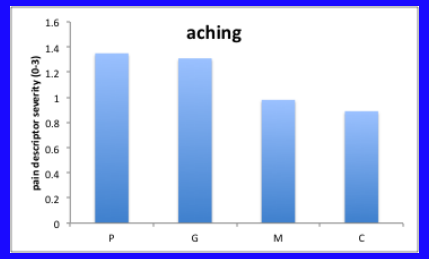


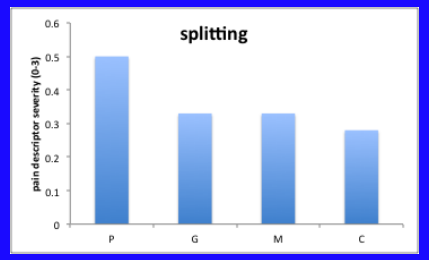












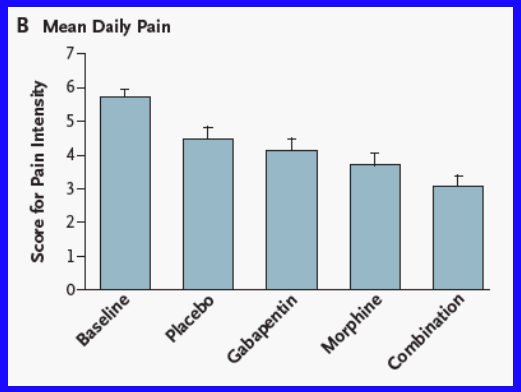
SF-MPQ Descriptors "congrouous" with primary outcome:

- Throbbing - Shooting - Sharp - Gnawing

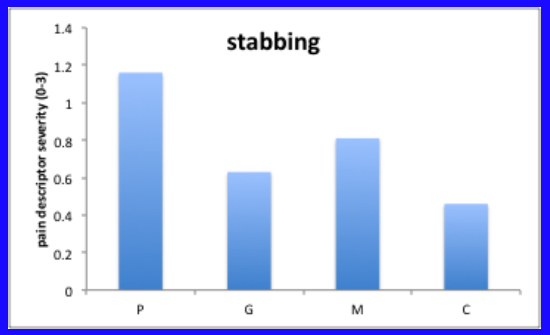
- Tender - Aching - Splitting

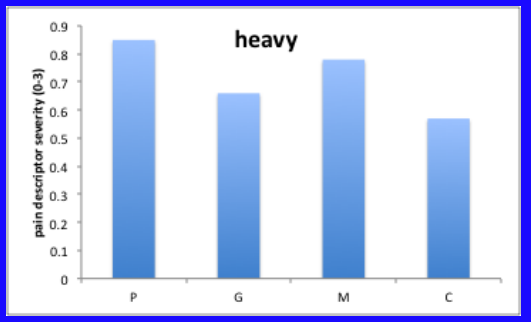
Deconstructing the analgesic response

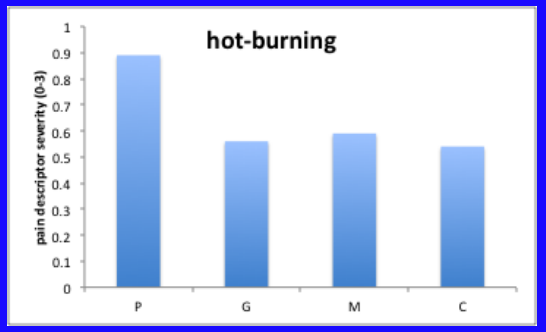
1^0 outcome:
0-10 NRS intensity

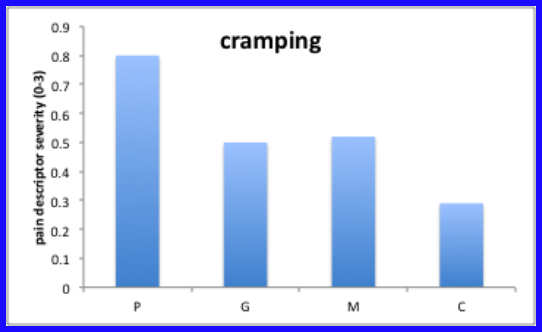


Gilron et. al., 2005









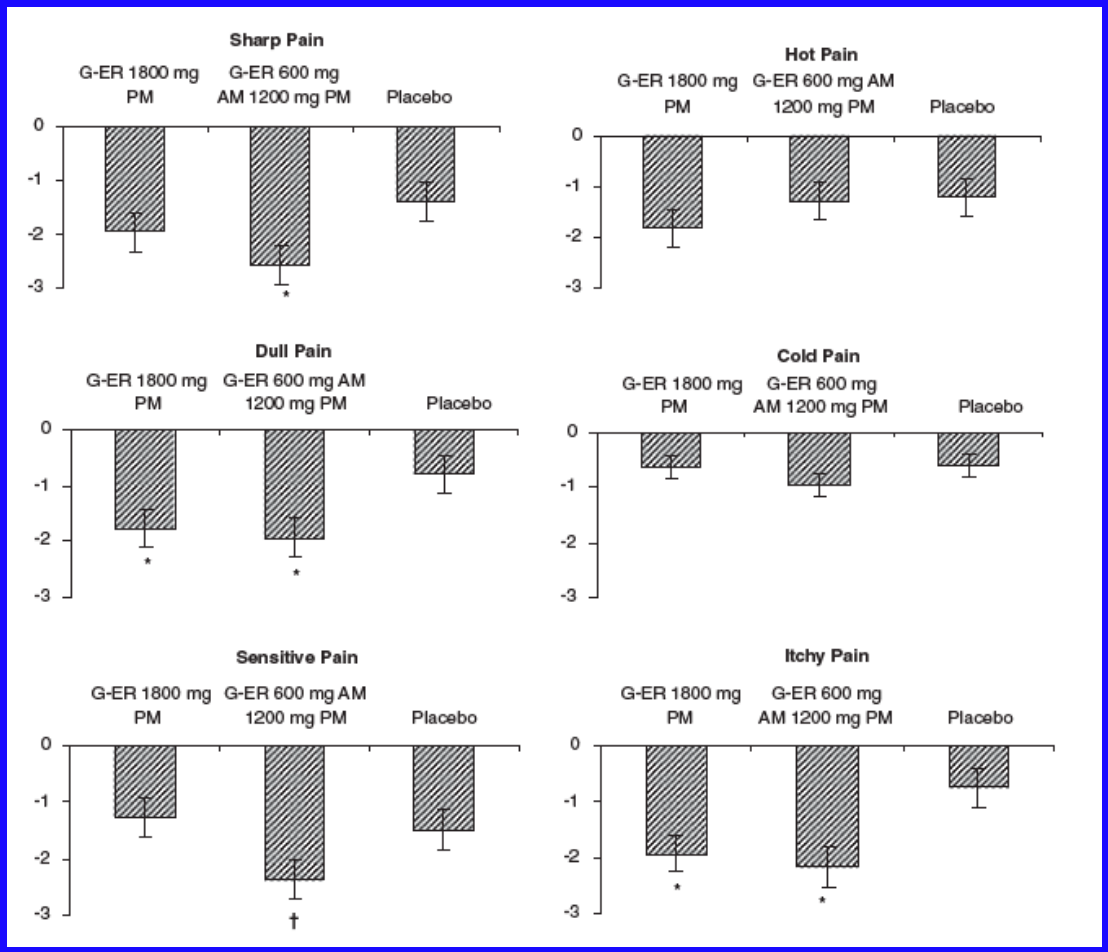
SF-MPQ Descriptors "incongrouous" with primary outcome:

- Stabbing - Heavy - Hot-burning - Cramping

Deconstructing the analgesic response

Assessment of Pain Quality in a Clinical Trial of Gabapentin Extended Release for Postherpetic Neuralgia

Mark P. Jensen, PhD, Yu-Kun Chiang, PhD,† and Jacqueline Wu, PhD‡*



Gabapentin-ER has the greatest effects on sharp, dull, sensitive & itchy pain.

Few effects were found for global ratings of intensity or unpleasantness, & for hot, cold, deep, or surface pain qualities.

Jensen et. al., 2009

Deconstructing the analgesic response

Rx: New! Pain-b-gone©

Approved for the treatment of ***gnawing***, ***splitting*** and ***fearfu***
pain (only).

Spontaneous *versus* evoked pain

- Pain after traumatic/surgical tissue injury:

- Pain evoked by movement often >100% more painful than “rest pain”;
- dynamic pain more strongly correlated with impaired functional recovery *(Gilron et. al., ‘02)*
- differential Tx response, e.g. NSAIDs effective for both, opioids much less effective for evoked pain
- Only ~40% of postoperative RCTs measure evoked pain *(Srikandarajah & Gilron, ‘11)*

- Evoked pain in chronic conditions (e.g. neuropathy, OA):

- Relative contribution of spontaneous vs. evoked symptoms not well described and likely variable *(Backonja & Stacey, ‘04)*
- If a new treatment selective against one or the other is evaluated, will such selectivity be identified by the classical 0-10 NRS?

Do we need an alternative 1^{0} outcome vs. "global" pain intensity?

- Proposal:

- For a variety of conditions (e.g. PHN, OA, lumbar stenosis etc.), develop a database which characterizes features with maximal & most frequent pain burden (e.g. night-time allodynia, morning stiffness, exercise-induce claudication)

- in addition to matching these features to study treatment target, also develop outcome measure which most reflects pain burden associated with the condition

- Problems?

- "customizing" outcome measures to condition or treatment would lead to +++heterogeneity across trials and hinder comparability
- this could be addressed by including a global pain intensity measure (e.g. 0-10 NRS) in all trials as a secondary outcome

Concentration-controlled titration to reduce pharmacokinetic variability

SINGLE ITEM SCORES ON THE NEUROPATHY OBSERVER SCALE DURING PLACEBO, PAROXETINE AND IMIPRAMINE

Medians are given and significant differences (Wilcoxon's test) are indicated.

	Placebo	Paroxetine	Imipramine
Pain	1.47	0.52	0.49 [a,b,c]
Paraesthesia	1.48	0.54	0.49 [a,b]
Dysaesthesia	0.75	0.48	0.03 [b,c]
Hypaesthesia	0.04	0.03	0.02
Nightly aggravation	1.49	0.52	0.04 [a,b,c]
Sleep disturbance	0.75	0.47	0.02 [b,c]

[a] Paroxetine significantly different from placebo.
[b] Imipramine significantly different from placebo.
[c] Imipramine significantly different from paroxetine.

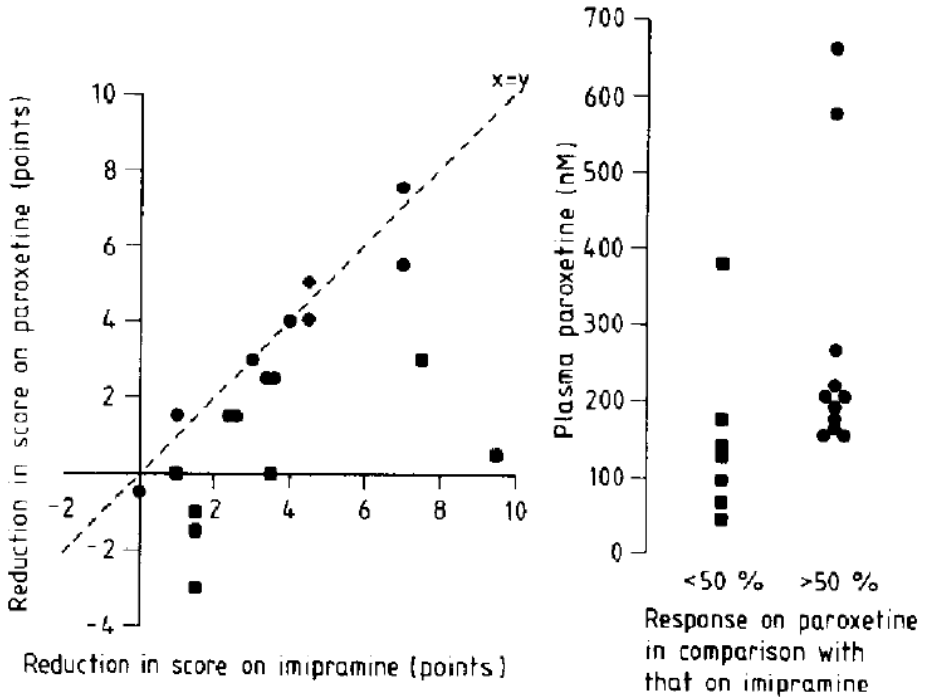


Fig. 1. Reduction in the scores on the neuropathy observer scale with paroxetine compared to the reduction with imipramine. ■, patients with a paroxetine response less than 50% of that with imipramine; ●, patients with a paroxetine response more than 50% of that with imipramine. A plot of plasma concentrations of paroxetine in these 2 groups of patients is inserted on the right.

Sindrup *et. al.*, Pain. 1990 Aug;42(2):135-44.

Summary

- Future improvements in trial methodology (e.g. careful attention to PK-PD, reducing measurement error, minimizing variability and bias) are likely to improve assay sensitivity and the informative value of POCTs
- However, current challenges in analgesic drug development warrant more extensive paradigm shifts in designs of POCTs of novel analgesics
- Future successes may require novel, multi-staged, trial designs which progressively adapt based on earlier results to guide ‘next stage’ modifications in target population, outcomes, dosing, treatment approach etc.
- Matching the mechanistic *specificity* of many novel treatment targets to the mechanistic *diversity* of most pain conditions may require recognition (& acceptance) that future analgesics may have narrower indications.