Accelerating the Development of Enhanced Pain Treatments
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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 clinicians may facilitate trial recruitment & future clinical Rx implementation

“Mechanism/phenomenon”- based
- e.g. tactile allodynia, mechanical hyperalgesia or pain on movement
- if study treatment can be matched to a discrete mechanism, Tx effect size and generalizability could be optimal
- more difficult to target for trial recruitment & future practice

Max, 1990; Woolf & Max, 2001
• 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.

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Maier et. al., PAIN 2010

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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.
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 (1⁰)
  but did reduce allodynia severity (day 1) & area (day 7)

• Nurmikko *et al.*, ‘07: “neuropathic pain & allodynia”
  - sativex reduced “global neuropathic pain” (1⁰) and also allodynia

-problems:
  1. Is the study Tx matched to the target mechanism?
  2. Is the primary outcome matched to the target mechanism?

• Astra Zeneca: “neuropathic pain & mech hypersens’y”
  - AZD2066 (NCT00939094-completed), 1⁰ outcome: “pain intensity”
mechanism vs. predictor of response

Is there a difference?

Attal et. al., 2004

Carroll et. al., 2010

Edwards et. al., 2006
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.
“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<sup>st</sup> outcome: 0-10 NRS intensity

**SF-MPQ Descriptors “congruous” with primary outcome:**

- Throbbing
- Shooting
- Sharp
- Gnawing
- Tender
- Aching
- Splitting

*Gilron et. al., 2005*
Deconstructing the analgesic response

10 outcome:
0-10 NRS intensity

SF-MPQ Descriptors “incongruous” with primary outcome:

- Stabbing
- Heavy
- Hot-burning
- Cramping

Gilron et. al., 2005
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 *fearful* 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.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Paroxetine</th>
<th>Imipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1.47</td>
<td>0.52</td>
<td>0.49</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1.48</td>
<td>0.54</td>
<td>0.49</td>
</tr>
<tr>
<td>Dyasaesthesia</td>
<td>0.75</td>
<td>0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypaesthesia</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Nightly aggravation</td>
<td>1.49</td>
<td>0.52</td>
<td>0.04</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>0.75</td>
<td>0.47</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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.**
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.