Improving Assay Sensitivity in Chronic Pain Clinical Trials

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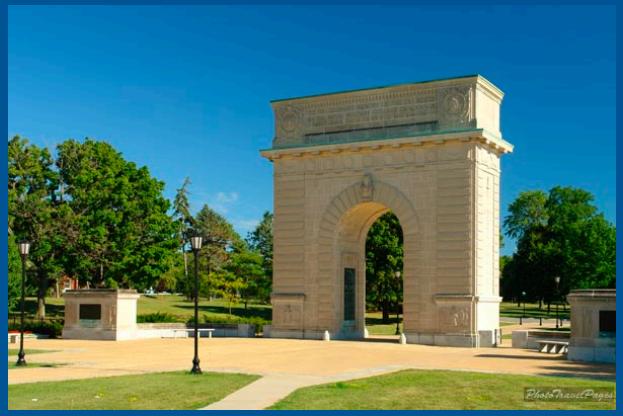

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Assay sensitivity: *"…the ability to distinguish an effective treatment from a less effective or ineffective treatment" Focus on methodology which limits "false negatives" and thus enhances "sensitivity".*

Prespecified analyses & hierarchy of endpoints

Primary outcome measure(s)

What does a priori designation really say about treatment effect?

- 2-arm, parallel, placebo vs. "drug X" (+ stable opioids) for cancer pain
- Measures: pain, BPI, MPQ, NPS, PGIC, AEs, opioid use
- Given that Tx may: produce its own **AEs**, **reduce opioid dose or opioid-related AEs**, and improve function…

What should the primary outcome be?
Pain intensity? Opioid dose? Integrated assessment?
Composite score including pain interference measures?

Dogma dictates we must decide *a priori* to prevent bias…

… but what do the data show?

TTX for Moderate to Severe Cancer Pain: A Randomized, Double Blind, Parallel Design Multicenter Study

Hagen et. al., J Pain Symptom Manage 2008

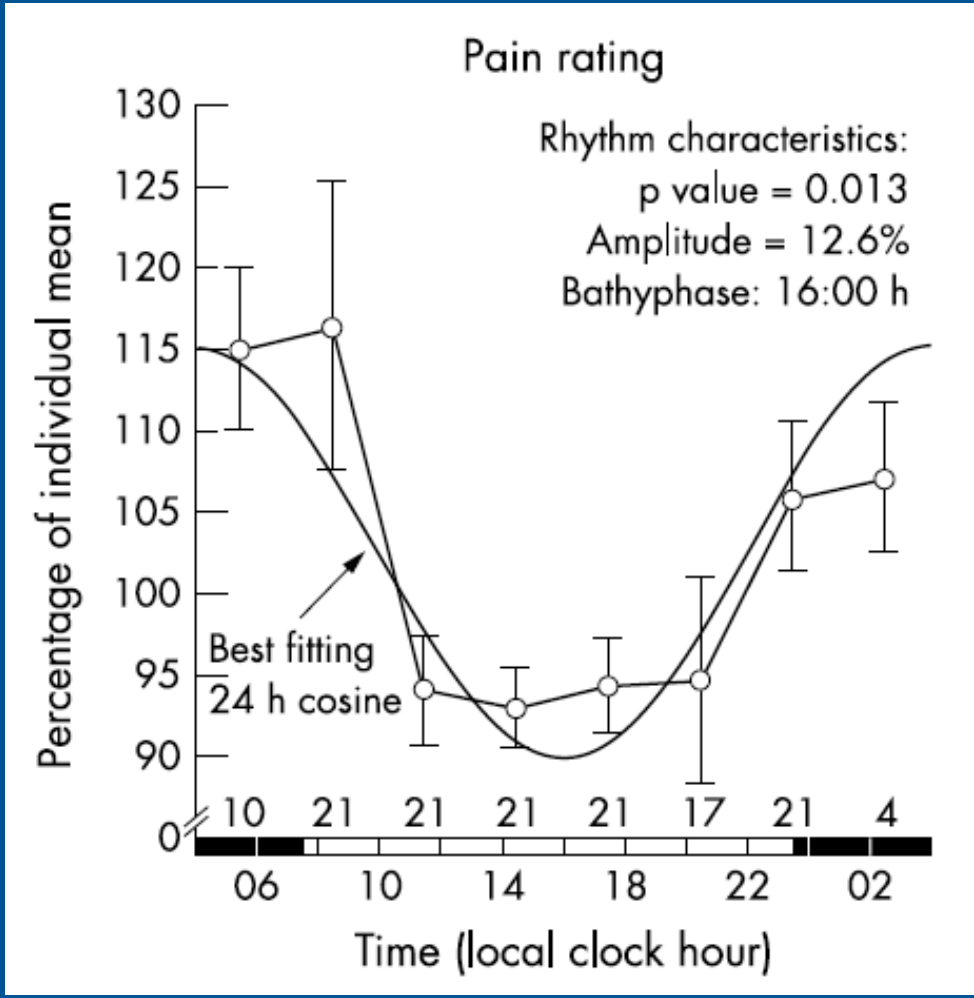
- *A priori* analysis: Proportion of responders (30% pain reduction from BL only if opioid doses <125% BL)
- *A priori* responders: TTX-16/38(42%) *vs*. Placebo-12/39(31%), ***P=0.425***
- *Post hoc* analysis: New responder definition:
  30% pain reduction **OR** >50% opioid reduction
  AND
  >30% improvement in BPI interference items
- *Post hoc* responders: TTX-17/38(45%) *vs*. Placebo-8/39(21%), ***P=0.043***

So, is this a truly negative trial?

Is there ever a role for semi-qualitative examination of RCT data? If yes, when?

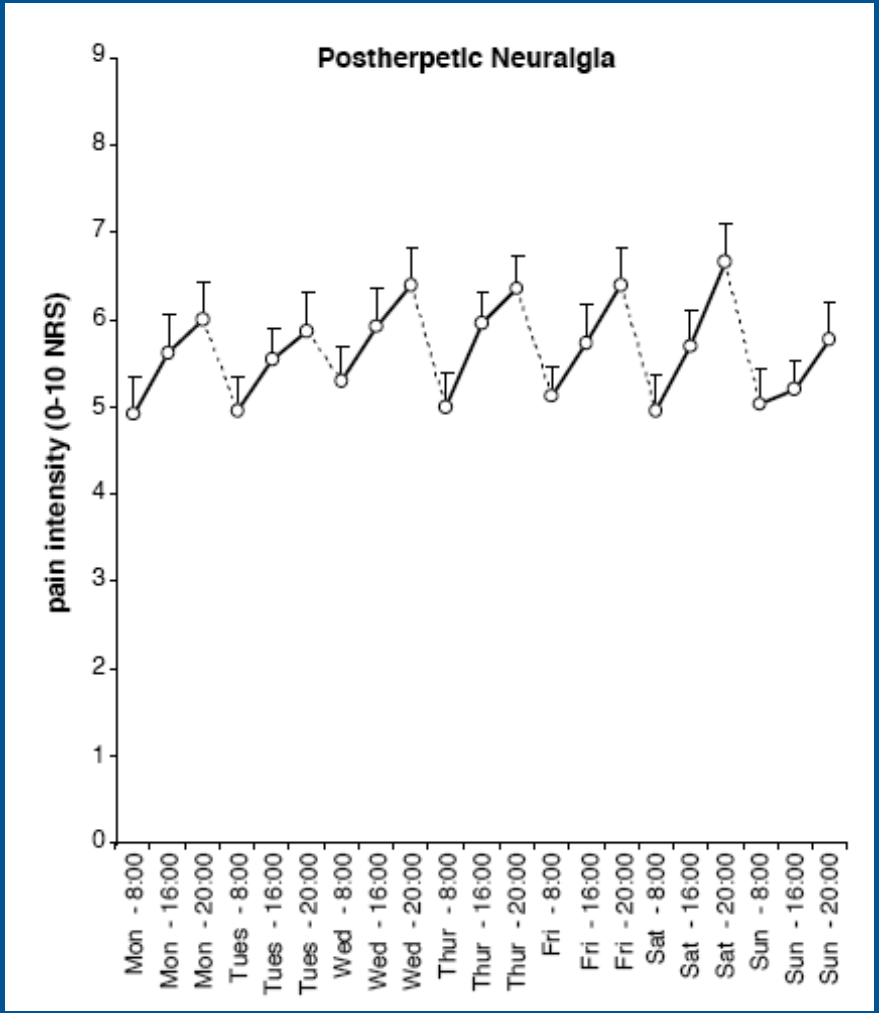
Increasing Reliability of Outcome Measurement

Circadian rhythm in pain, stiffness, and manual dexterity in rheumatoid arthritis



Bellamy et. al., Ann Rheum Dis. 1991 Apr;50

Chronobiological characteristics of painful diabetic neuropathy and postherpetic neuralgia



Odrcich et. al., Pain 2006

Dr. Jensen

Increasing Reliability

Standardize Procedures

- Same time

- Same measure

- Same person

- Same place

- *No studies have tested the effects of these on reliability/responsivity*

Reducing variability of outcome measures

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.

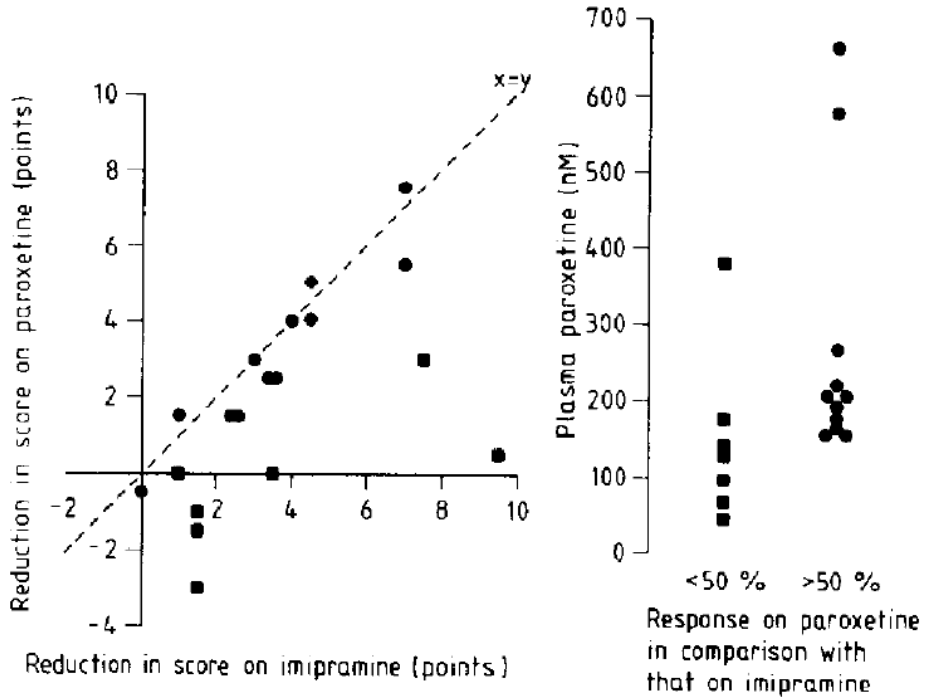


Fig. 1. Reduction in the scores on the neuropathy observer scale with paroxetine compared to the reduction with imipramine. ■, patients with a paroxetine response less than 50% of that with imipramine; ●, patients with a paroxetine response more than 50% of that with imipramine. A plot of plasma concentrations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

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

Responses to placebo

The powerful placebo. *Beecher HK, JAMA 1955*
Friend or Foe?

• In some RCTs, as many as 50% of placebo recipients reported >30% pain reduction; Therefore, some might challenge the **exclusion of placebo responders** as unacceptably **limiting generalizability**

• What if we could **predict** who will be a placebo responder? (e.g. Subjects with higher OA flare intensity more likely to respond to placebo. *Scott-Lennox et. al., Arthritis & Rheumatism 2001*)

• Balancing treatment groups by stratifying treatment randomization according to various factors may serve to minimize bias. *Knipschild et. al., J Clin Epidemiol 2001.*
e.g. stratify treatment randomization according to placebo run-in responders? multicenter sites? (some more nurturing than others)

Active Control Trial Designs

Active comparators as "positive control" in placebo-controlled RCT

Drawbacks

- Increased trial complexity and cost
- Trial results could be misleading if previous experience with comparator by subjects leads to "enrichment" and thus bias in favor of comparator
- "Competitive risk" that study drug is outperformed by comparator

Active comparators as "positive control" in placebo-controlled RCT

- Currently, inclusion of a placebo treatment in chronic pain trials remains acceptable

- Unlike a non-inferiority trial, inclusion of an active comparator with known efficacy may serve to confirm (or refute) assay sensitivity in the event of *no difference* between study drug and placebo

- "Adolor shares fall on pain drug study results" Associated Press, June 2010
"ADL5747 and ADL5859 failed to reduce pain in the 400-person study",
"… a higher-than-expected reduction in pain for patients taking placebo."
"…also showed no significant difference between the placebo and OxyContin."

Pre-recommendation comments

• Current trial methods are imperfect; problems with assay sensitivity have impeded the development of new pain treatments

• Hopefully, methods can be refined to improve assay sensitivity, HOWEVER, any changes must consider “costs” and possible threats to trial validity (N.B. Don’t lose sight of the distinction between a “failed trial” and a “useless treatment”)

• Areas for future research (retrospective e.g. using “REPORT”; prospective e.g. trials/studies to test new methods):
- role of active comparators in placebo-controlled superiority RCTs
- “handling” of placebo response; identify responders, ?stratify randomization?
- role of electronic data capture and more explicit instructions for patient report measures
- impact of primary outcome measure on trial outcome
- role of PK assessments and concentration-targeted dose titration to reduce variabliity