

# Meaningful Change and Meaningful Endpoints in Pain Clinical Trials

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# Overview

How much change in pain intensity is meaningful?

What is a reasonable endpoint goal for pain treatment?

# Meaningful change: Chronic Pain

## 0 – 10 NRS

Farrar JT, Young, JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-158.

Hanley MA, Jensen MP, Ehde DM, Robinson LR, Turner JA, Smith DG. Clinically significant change in pain intensity ratings in persons with spinal cord injury or amputation. *Clin J Pain*, under review.

## 10cm VAS

Hägg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J.* 2002;12:12-20.

Forouzanfar T, Weber WEJ, Kemler M, van Kleef M. What is a meaningful pain reduction in patients with Complex Regional Pain Syndrome Type 1? *Clin J Pain* 2003;19:281-285.

# Farrar et al., 2001

- Chronic pain (DPN, PN, OA, LBP, FM), N = 2724.
- Pregabalin vs. placebo study.
- Treatment time: 5 – 12 weeks.
- Criterion = Patient's global rating of change:
  - Very much improved
  - Much improved
  - Minimally improved
  - No change
  - Minimally worse
  - Much worse
  - Very much worse

# Farrar et al., 2001

Change associated with:

- Much improved: 2/10; 30%
- Very much improved: 4/10; 50%

Receiver operating characteristic curve analysis:

- Minimally improved +: 1.00/10; 15%
- Much improved +: 1.74/10; 28%
- Very much improved: 2.76; 47%

Absolute change more strongly affected by baseline pain than percent change. No impact of dx, tx, tx duration, age, or sex.

# Hanley et al., 2004

- Chronic pain in persons with disabilities (SCI, AMP), N = 116.
- Amitriptyline vs. placebo study.
- Treatment time: 6 weeks.
- Criterion = Patient's rating of meaningfulness of change:
  - My pain decreased to a meaningful extent
  - There was some decrease in my pain, but not enough to be meaningful
  - There was no change in my pain
  - There was some increase in my pain, but not enough to be meaningful
  - My pain increases to a meaningful extent

# Hanley et al., 2004

Change associated with:

- Meaningful decrease: 1.86/10; 36%
- Decrease, not meaningful: 1.12/10; 23%

Both absolute and percent change affected by baseline pain.

Age also associated with the level of change needed for it to be deemed meaningful (older patients, more change needed; 2.4/10 vs. 1.2).

No impact of dx, tx, or sex.

# VAS research

Forouzanfar et al., 2003

- Complex Regional Pain Syndrome type 1 (N =61)
- Spinal cord stimulation.
- Assessments at baseline, 6-, 12-, and 24-months.
- Worst ever | Much worse | A little worse | Not changed | A little improved | Much improved | Best ever
- ROC analyses: 3cm, 50% (all three assessment points)
- Change associated with each rating
  - Not changed: 14% - 23%
  - A little improved: 26% - 31%
  - Much improved: 58% - 71%



# VAS research

Hägg et al., 2002

- “Severe” LBP (N =289).
- Fusion surgery (3 types) vs. standard care.
- Assessments at baseline and 2 years posttreatment.
- Much better   Better   Unchanged   Worse
- Change associated with:
  - “Better” (21mm) – “Unchanged” (3mm) = 18mm;
  - “Much better” (43mm) = Unchanged = 40mm.
- Percent not examined.

# Acute Pain (breakthrough and postop)

Farrar et al. (2000). ROC (request for rescue dose): 2/10, **33%**.

Farrar et al. (2003). ROC (request for rescue does): 2/10, **33%**.

Jensen et al. (2003). Little relief: 9mm – 13mm, 13% - 18%;  
Some relief: 20mm – 27mm, **36% - 41%**; A lot: 44mm,  
64% - 66%; Complete: 62mm - 67mm, 99% - 100%.  
Baseline pain influenced change scores.

Cepeda et al. (2003). Minimal improvement: 1.3/10, 20%;  
Much improvement: 2.4/10, **35%**; Very much  
improvement: 3.5/10; 45%. Baseline pain influenced  
change scores.

# Conclusions

How much change is necessary for that change to be deemed meaningful? *It depends, on*

- Baseline pain for both absolute and % change.
- Criterion used.
- Age (one study)? Duration of treatment (weeks vs. years)?
- Not influenced by sex, dx, or treatment condition w/i study.

Chronic pain:

Range = 1.7 – 2.0/10, 28% - 36% for 0 – 10 NRS.

Range = 50% for 100mm VAS (CRPS 1; 6-24 months).

Acute pain:

Range = 2.0 – 2.4/10, 33% - 35% for 0 – 10 NRS.

Range = 20mm – 27mm, 36% - 41% for 100mm VAS.

# Recommendations

Percent is better than absolute in most situations.

- Except when pretreatment pain is low,  
(say,  $\leq 3$ ).

For the 0 – 10 NRS, **30%** change is a reasonable standard at this point in time;

But future research may show that is is low (or that somewhat different standards are needed for different pain problems).

# Reasonable endpoint

Patients may care more about the final endpoint than the amount of change.

If so, what is a reasonable endpoint goal? 0/10?  
 $\leq 2/10$ ?  $\leq 4/10$ ?  $\leq 5/10$ ?

Need an operational definition of “mild” pain.

- Pain termed “mild” by the majority of patients
- Pain that has relatively little impact on functioning.

# Pain classified by patients

## Cepeda et al., 2003

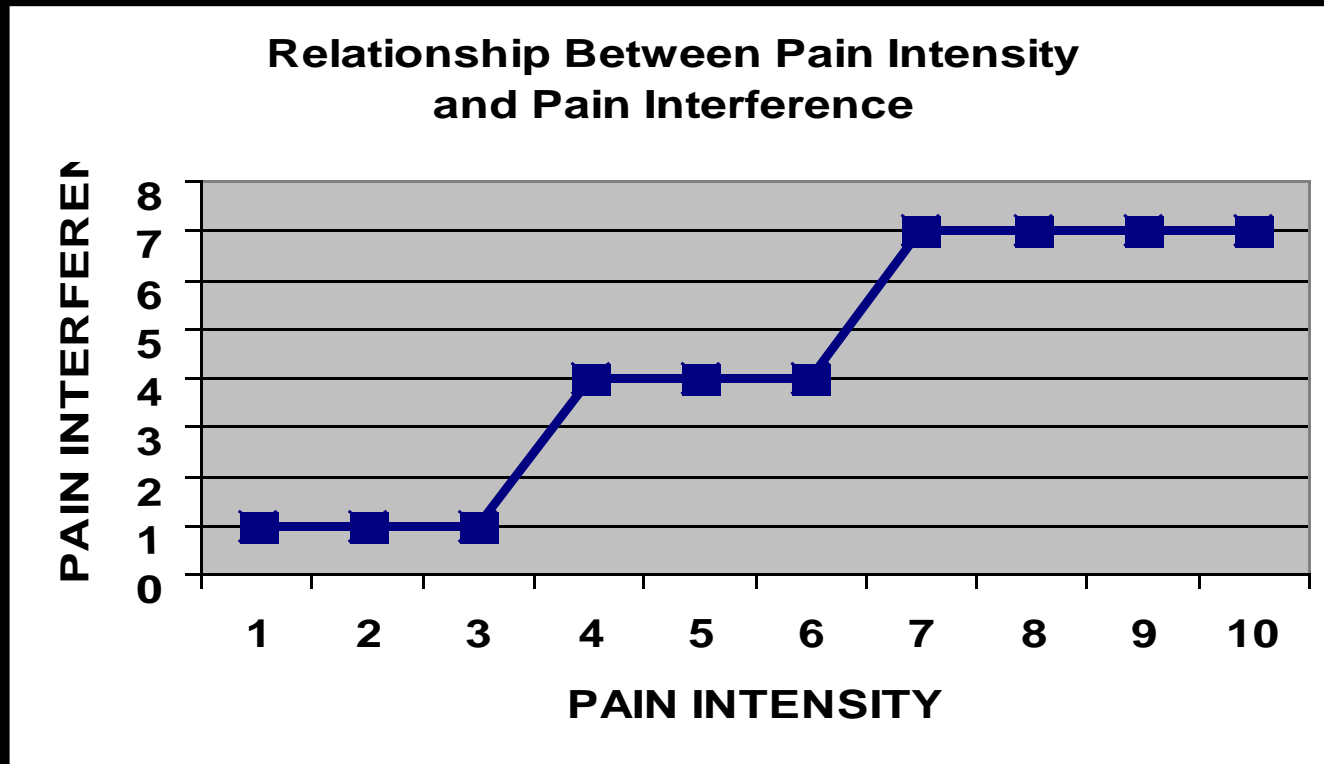
- N = 700 postsurgical patients
- “Moderate” pain median = 6/10.
- “Severe” pain median = 8/10.
- “Mild” pain = not specified.

# Pain classified by patients

## Jensen et al., 2003

- N = 248 postsurgical patients (knee surgery/laparotomy)
- “None” range:  $\leq .05\text{cm}$ .
- “Mild” range:  $.06\text{cm} - 4.4\text{cm}$ .
- “Moderate” range:  $4.5\text{cm} - 7.4\text{cm}$
- “Severe” range:  $7.5\text{cm} - 10.0\text{cm}$ .

# Association with functioning





# Association with functioning

## Serlin et al., 1995

- N = 1897 individuals with cancer pain from four countries (USA, France, China, Philippines).
- Criterion: BPI interference score.
- CP46 optimal (1-4 mild, 5-6 moderate, 7+ severe).
- Not impacted by country.

# Association with functioning

## Jensen et al., 2001

- N = 205 individuals with acquired amputation.
- Criterion: 0 – 10 NRS pain interference.
- CP46 optimal for back and general pain.
- CP47 optimal for phantom limb pain (but CP46 close).

# Association with functioning

## Zelman et al., 1995

- N = 194 individuals with LBP (96) and OA (98).
- Pain intensity at screening  $\geq 4/10$ , 14%  $< 4$  at part.
- Criterion: BPI interference score.
- CP5 optimal for both samples.
- CP58 optimal for LBP (CP56, CP57 similar).
- CP57 for OA (CP56, CP58 similar).
- Cutpoints different for other functioning/impact measures (Roland, SF-36, Oswestry, WOMAC).

# Association with functioning

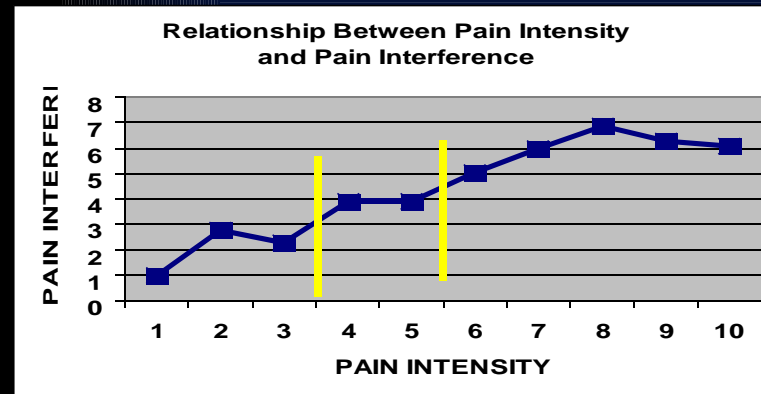
## Mendoza et al., 2004

- N = 266 postoperative (CABG) patients.
- Criterion: BPI interference score.
- CP46 optimal for 5/11 assessment days.
- CP36 (3 days), and CP47 (3 days) also optimal.
- Selected CP46 as “most optimal, most of the time.”

# Association with functioning

## Hanley et al., 2004

- N = 174 patients with SCI and pain.
- Criterion: 0 – 10 NRS interference rating.
- CP36 optimal.



# Conclusions

- Some intensity levels clearly mild (1-3), moderate (5-6), and severe (8-10).
- Classification of 4/10 and 7/10 less clear; depends on sample.

# Recommendations

- CP46 seems most reasonable.
- Recommend that “Pain  $\leq 4/10$ ” be a reasonable endpoint goal in clinical trials (recognizing that this might change to  $\leq 3$  for some populations as more is learned).
- Recommend that “Percent patients who change classification (from moderate to mild, severe to moderate)” be explored as an outcome metric.