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.


10cm VAS


- 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.
- Amitrityline 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%
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.
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, <= 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? <= 2/10? <= 4/10? <= 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: <= .05 cm.
- “Mild” range: .06 cm – 4.4 cm.
- “Moderate” range: 4.5 cm – 7.4 cm
- “Severe” range: 7.5 cm – 10.0 cm.
Association with functioning

Relationship Between Pain Intensity and Pain Interference

PAIN INTENSITY

PAIN INTERFERENCE

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8
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.
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.”
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 <= 4/10” be a reasonable endpoint goal in clinical trials (recognizing that this might change to <=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.