ANALGESIC SOLUTIONS

Improving Assay Sensitivity in Analgesic Proof-of-Concept Studies: Osteoarthritis

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ADEPT, Bermuda, March 25, 2011

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Objectives

- To present a conceptual framework for approaching the problem of assay sensitivity
- To provide examples of efforts to improve assay sensitivity, focusing on osteoarthritis

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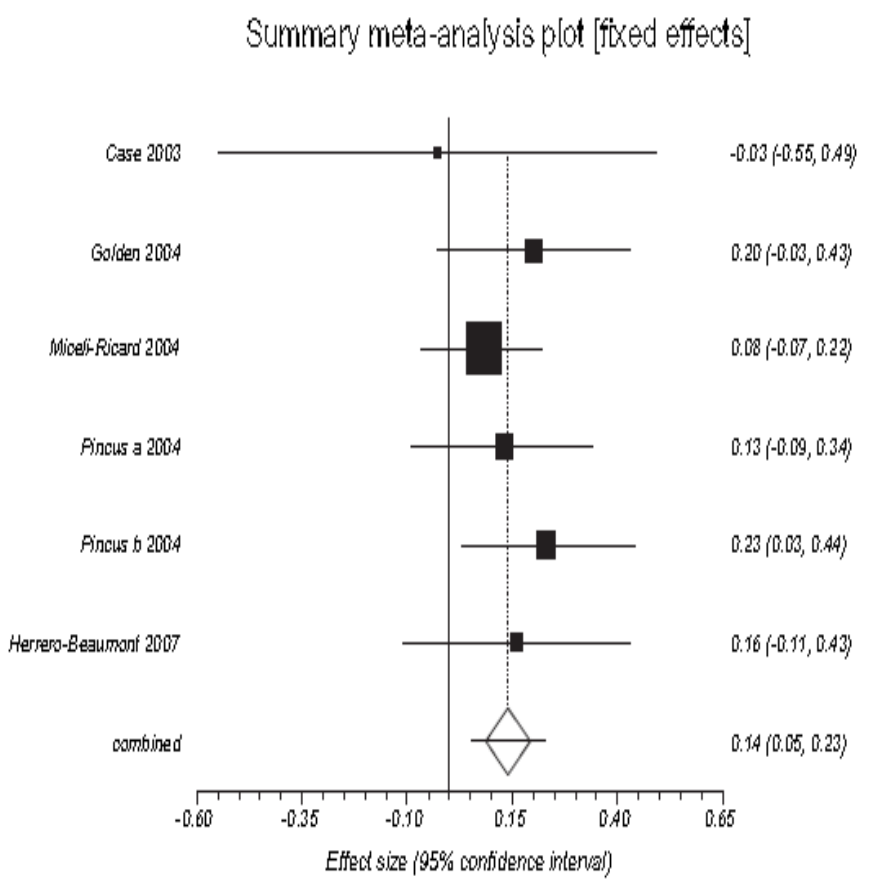
Why do effect sizes of identical treatments differ across studies?



- Actual biological effect of drug differs when studied by different authors
- Random chance: God rolls dice in our studies
- Aspects of study design or conduct influence observed effect size

Zhang et al, Osteoarthritis & Cartilage, 2010

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Assay Sensitivity

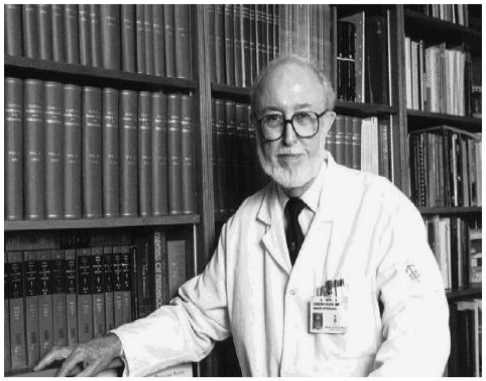
"a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment"

$$\frac{Pain_{ACTIVE} - Pain_{PBO}}{Std\ Dev_P}$$

International Conference on Harmonization. E10: Choice of control groups and related issues in clinical trials.

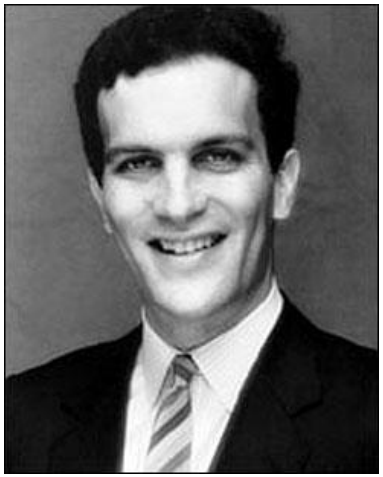
Abraham Sunshine
January 3, 1928–January 2, 2007

Ray Houde
(1916-2006)



Louis Lasagna
(1923-2003)

Mitchell B. Max
(1949-2008)



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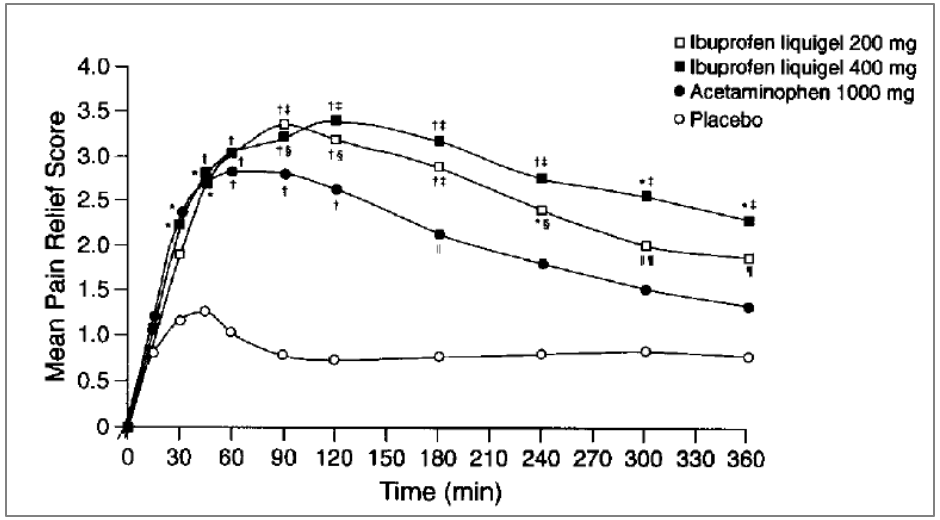
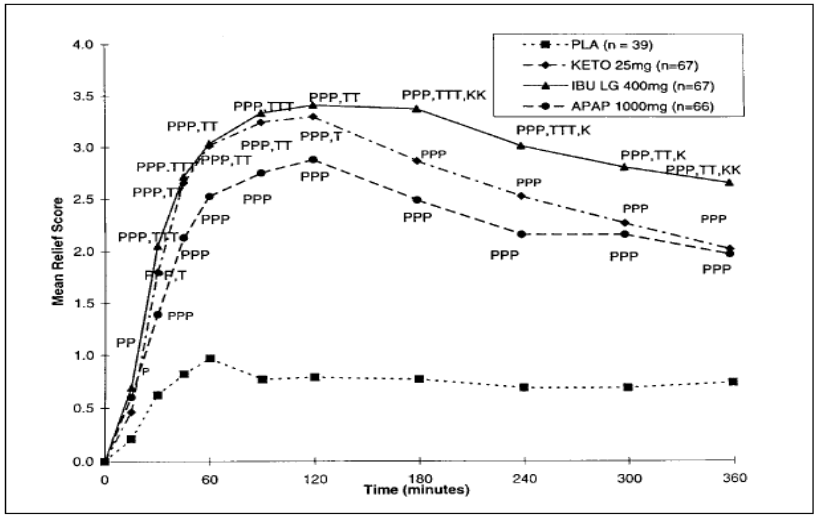
Ibuprofen Liquigel 400 mg for Dental Pain





Hersh E, et al, Clin Ther, 2000; Olson N, et al, J Clin Pharm, 2001

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Relative Standard Effect Size

SPID6 Ibuprofen liquigel 400mg vs. placebo:

	Hersh	Sunshine
Delta	7.61	9.17
SD	4.85	4.5
SES	1.57	2.04

Sunshine has 30% higher SES
(Equivalent to reducing sample size
from 100/arm to 60/arm)

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Pregabalin vs. Placebo in Inguinal Herniorrhaphy

	Lotus Research (n = 126)	All 24 Other Sites (n = 274)
Primary endpoint: Δ	0.81	0.56
SD	2.25	2.56
SES (Δ/SD)	0.360	0.219
N for 80% power, alpha = 0.05	244	658
Subjects enrolled per per month	23.2	0.75
Overall Performance (time to 80% power)	10.5 months*	36.6 months **

***utilizing one site at Lotus** ****utilizing 24 non-Lotus sites in concert**

Singla N, American Pain Society, 2010

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Implications

- The standardized effect size of a treatment is not fixed, but elastic depending on methodologic factors that determine assay sensitivity
- We can figure out what those methodologic factors are
- We can intentionally implement them in clinical trials to increase assay sensitivity

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Approaches

- Meta-analysis
  - By study
  - Within-patient
- Experimental

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Reasons for Failure: Opioid Trials

- Trial structure
  - Crossover and withdrawal better than parallel treatment
- Dosing
  - Titration better than non-titration
  - Flexible better than fixed
- Concomitant analgesics
  - Prohibited better than allowed
- Rescue
  - Prohibited better than allowed
- Primary endpoint
  - AUC better than landmark
- Number of sites
  - The fewer the better

Katz N, et al, Neurology, 2005

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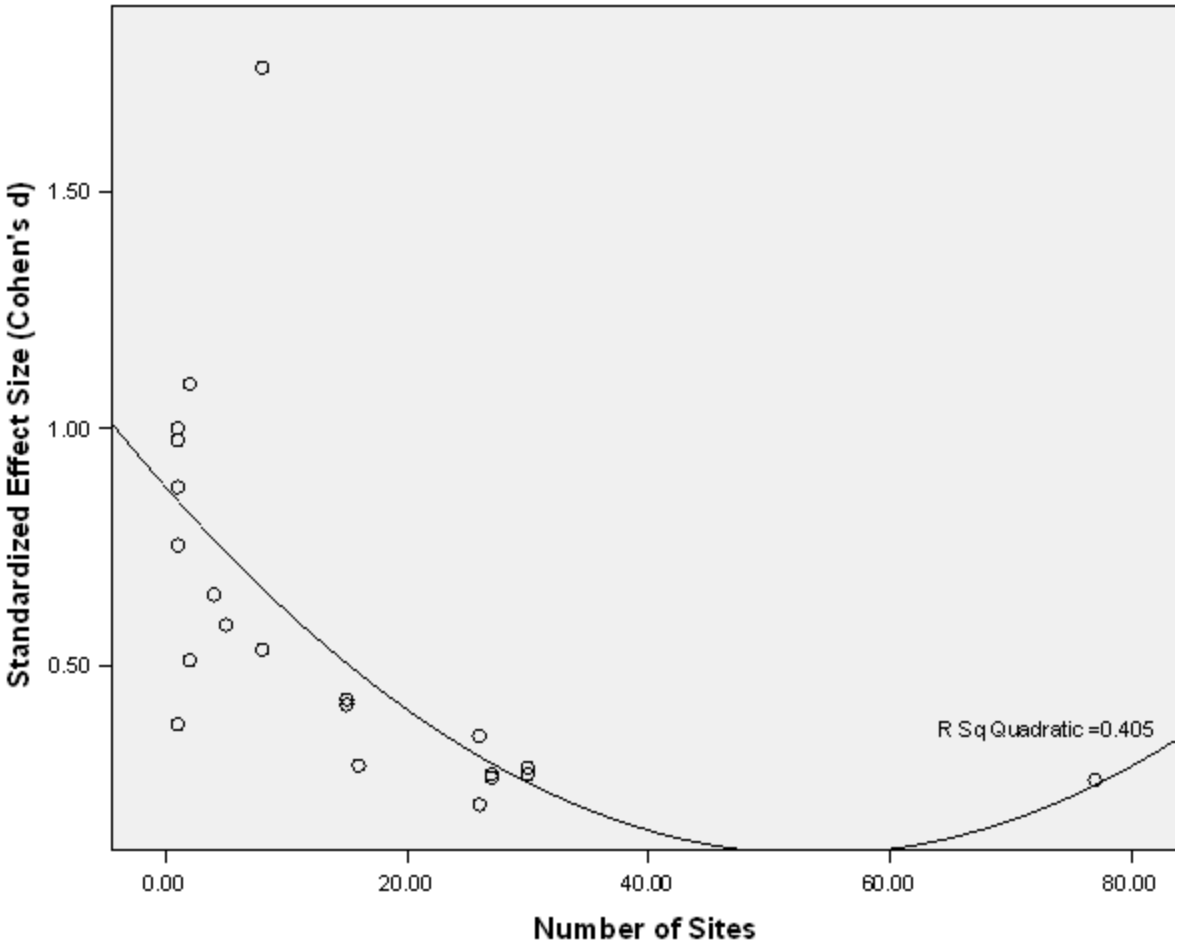
Standardized effect size vs. number of sites, opioid trials



- Decreasing SES from 1 to 0.25 can increase sample size requirements from 20 to 250 patients/arm

Adapted from Katz N, et al, Neurology, 2005

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Methodologic Factors

Study Level

- Study structure
- Number of arms
- Duration
- Number of visits
- Baseline duration
- Dose, administration
- Rescue meds
- Concomitant analgesics
- Protocol concealment
- Site training
- Investigator experience

Patient Level

- Diagnosis
- Pain duration
- Co-morbidities
- Psychiatric status
- Concomitant analgesics
- Demographics
- Baseline pain intensity
- Baseline pain variability
- Diary compliance
- Expectation of pain relief
- Previous experience

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Predictors of positive studies: neuropathic pain, n=90 studies

Table 3 Logistic regression model predicting clinical trial outcomes from study characteristics (n = 90)*

Placebo response added to initial model‖					
Medication response	0.15	0.04	0.001	1.16	1.07, 1.25
Sample size	0.03	0.01	0.003	1.03	1.01, 1.05
Year of publication	−0.08	0.08	0.292	0.92	0.78, 1.08
Study design§	−0.84	0.99	0.400	0.43	0.06, 3.04
Pain condition¶	0.91	1.27	0.474	2.48	0.21, 29.76
Placebo response	−0.24	0.06	0.001	0.79	0.70, 0.89

Katz J, et al, Neurology, 2008

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Sample size requirements to detect differences in SES by methodologic feature

Difference in SES	Total N of studies	Total N of Patients
0.1	74	12561
0.2	20	3142
0.3	12	1398
0.4	8	787
0.5	6	505

Increasing SES from 0.3 to 0.4 can decrease sample size requirements **per arm** from 175 to 100

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Meta-analytic methods

- Meta-analysis can shed light on the relationship between methodologic features and study outcome
- Databases will need to be large, and include within-patient data
- We should be looking for trends and testing candidate approaches experimentally

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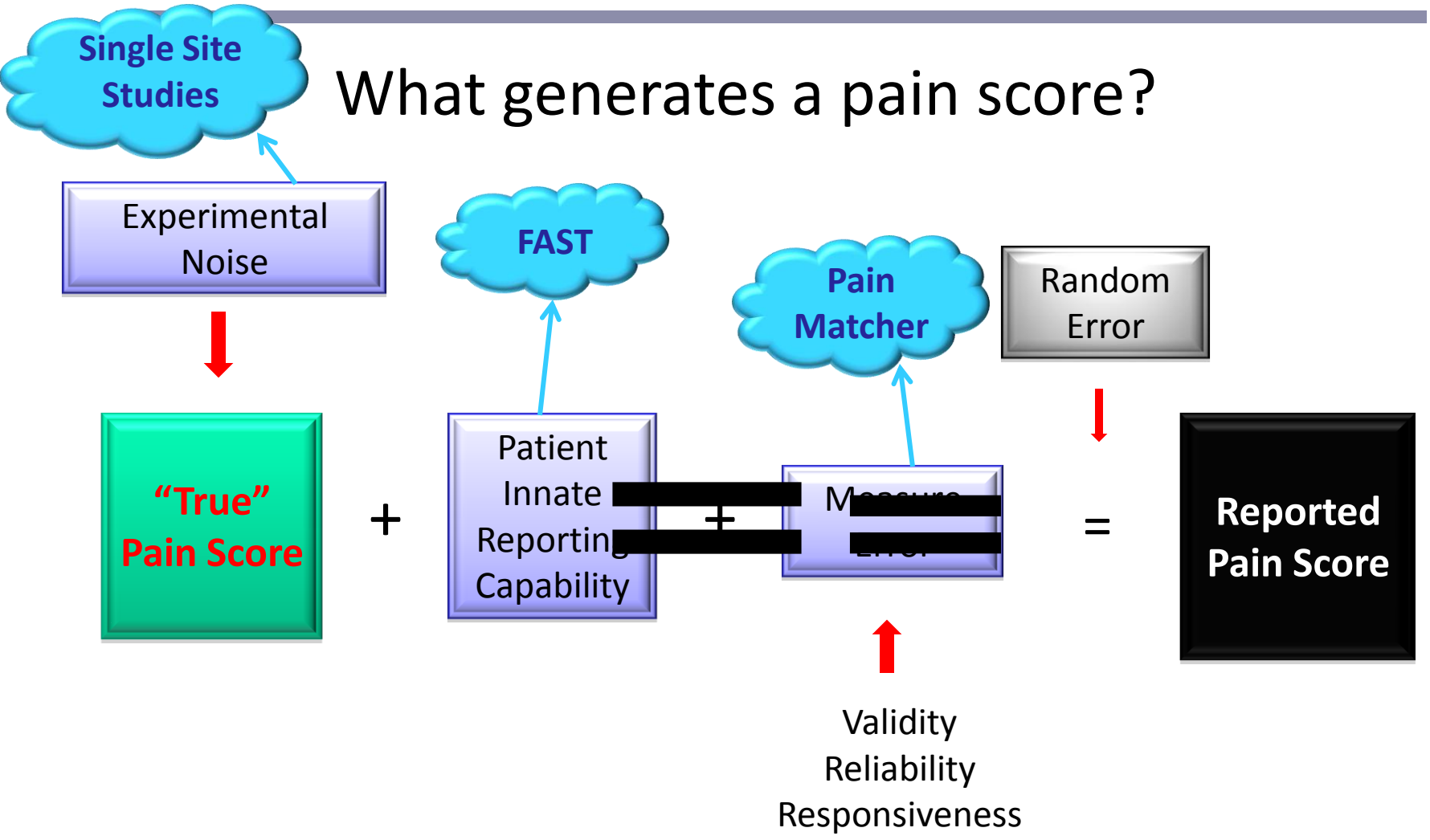
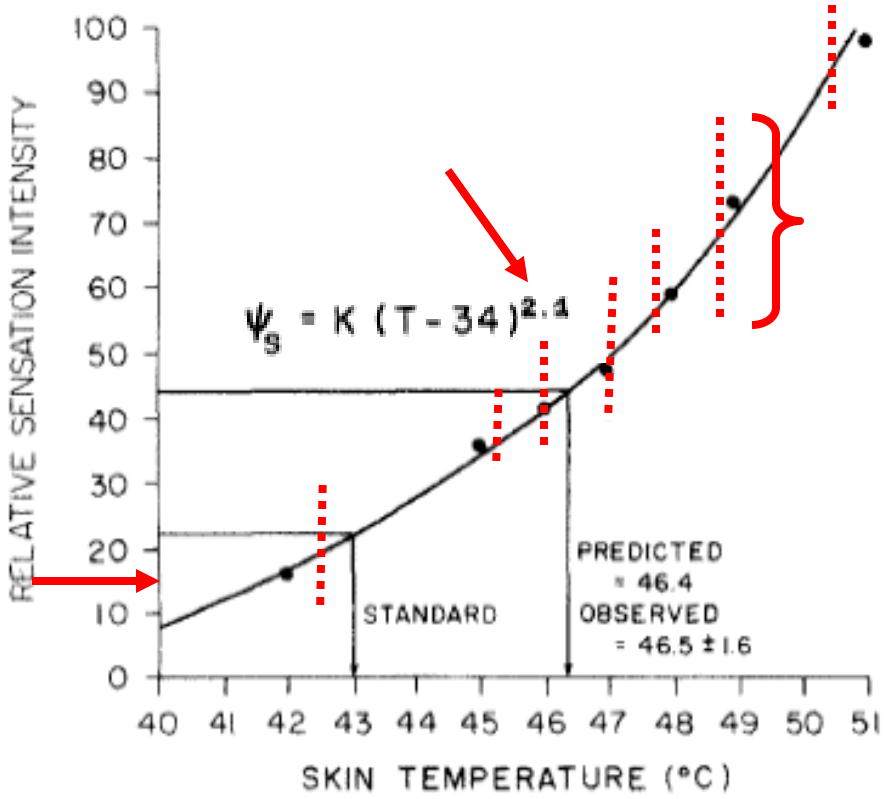
Experimental Approaches



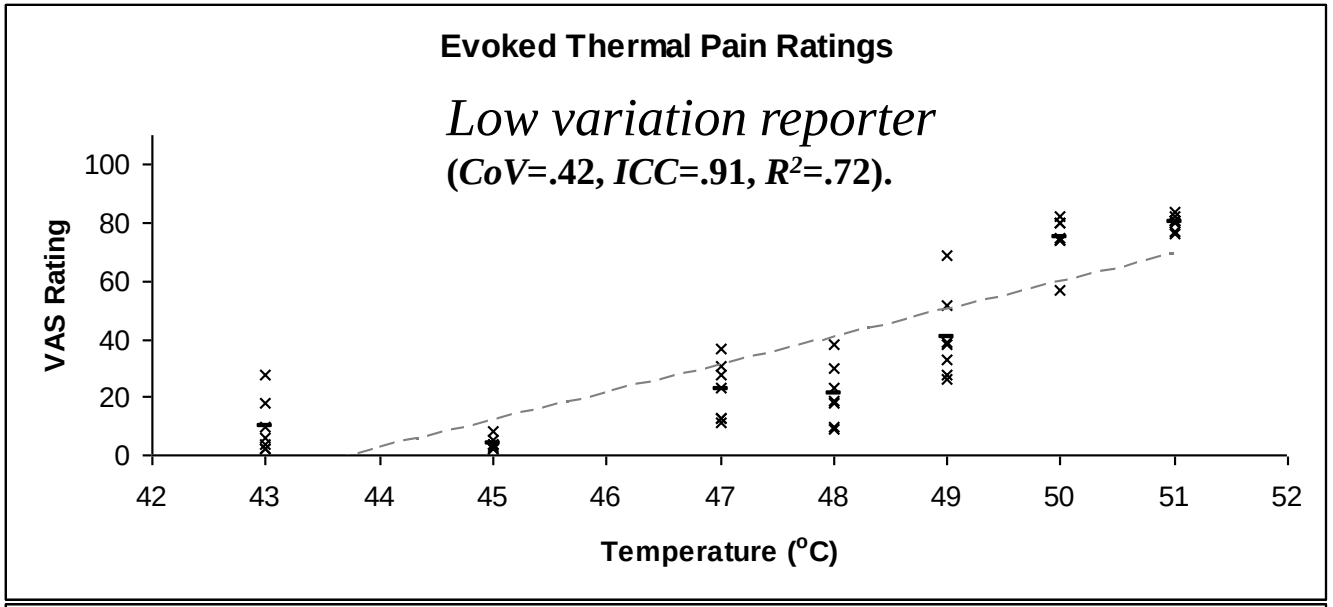
Psychophysical Assessment(Φ)

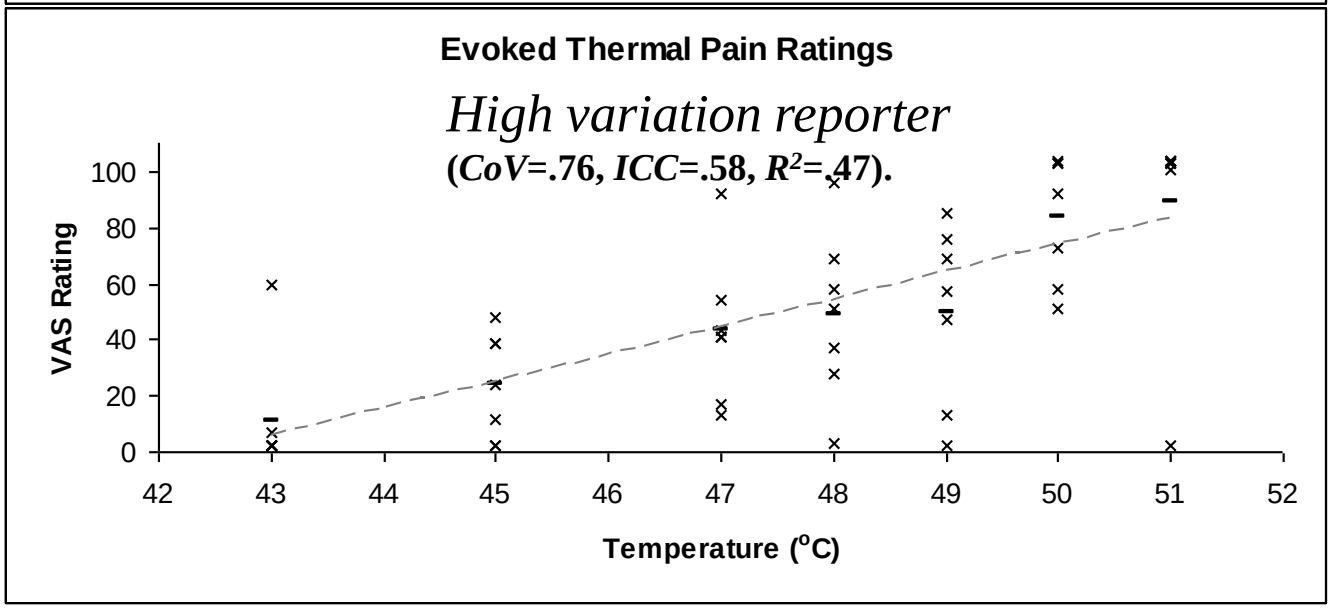
Experimental Pain Rating

Subjects rate 7 *heat* stimuli for pain level 7 times using VAS



Psychophysical Profile Samples Φ





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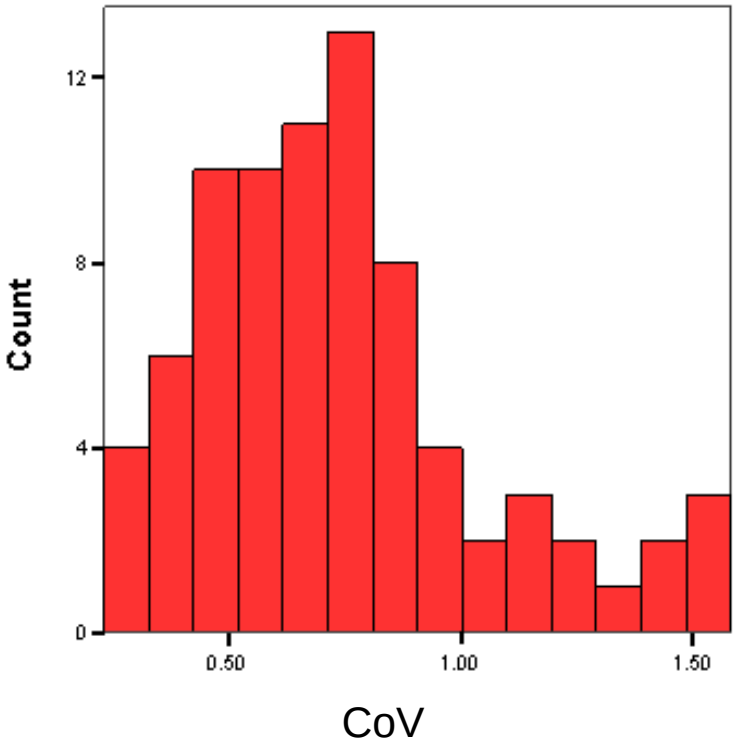
Frequency Plots for Pain Reporting Skill



N= 79
Mean = .74
SD= .31

Subjects demonstrated a large range of performance in pain reporting skill as indexed by CoV, ICC, and R^2.

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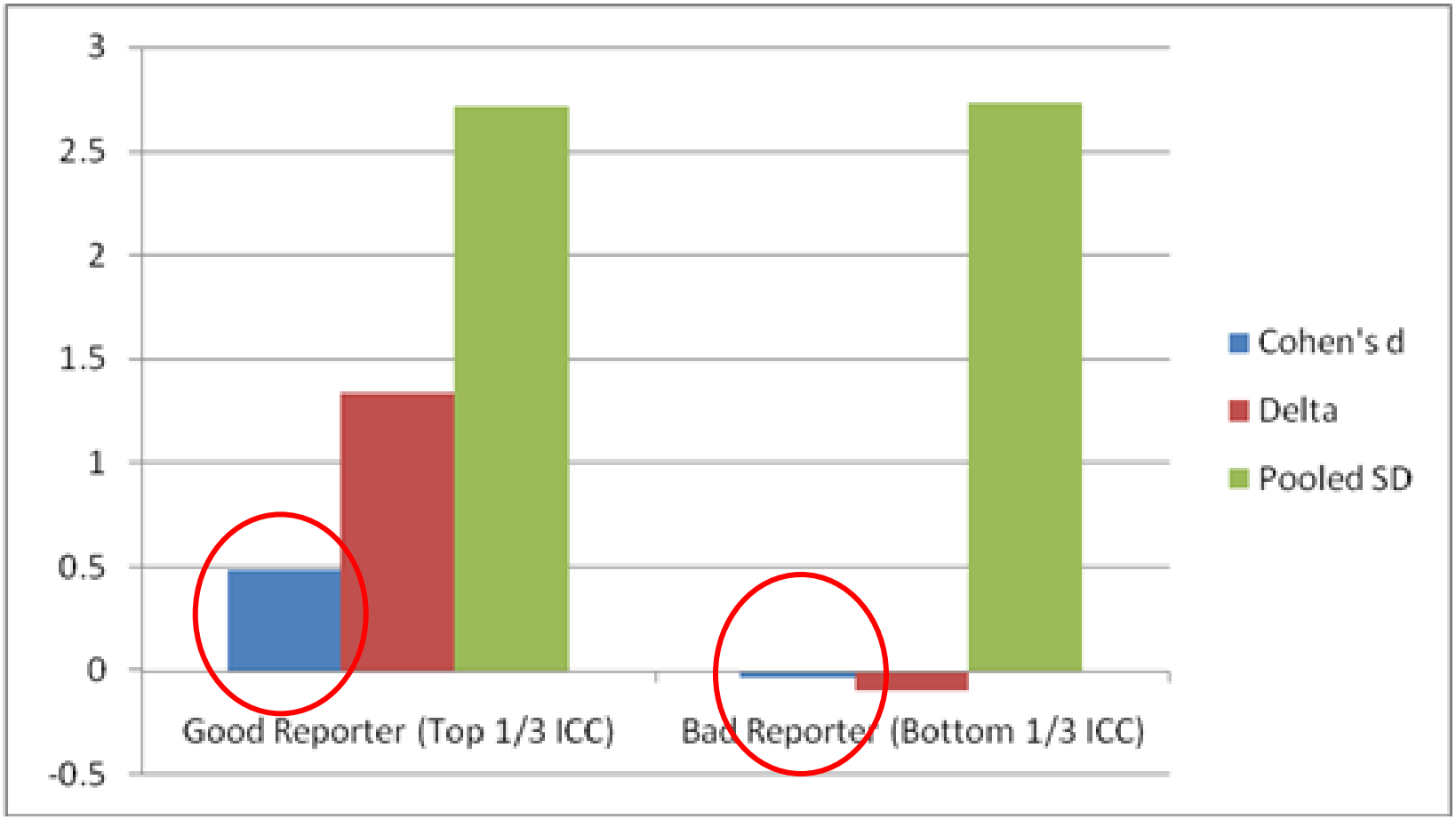
Pre- vs. post-exercise VAS scores in “good” vs. “bad” pain reporters



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Stay Tuned

- Single-site POC study in knee OA recently completed
- FAST assessment demonstrated to be reliable
- After excluding “high variability” pain reporters, NSAID separated from placebo in 31 subjects on primary endpoint of staircase-evoked pain

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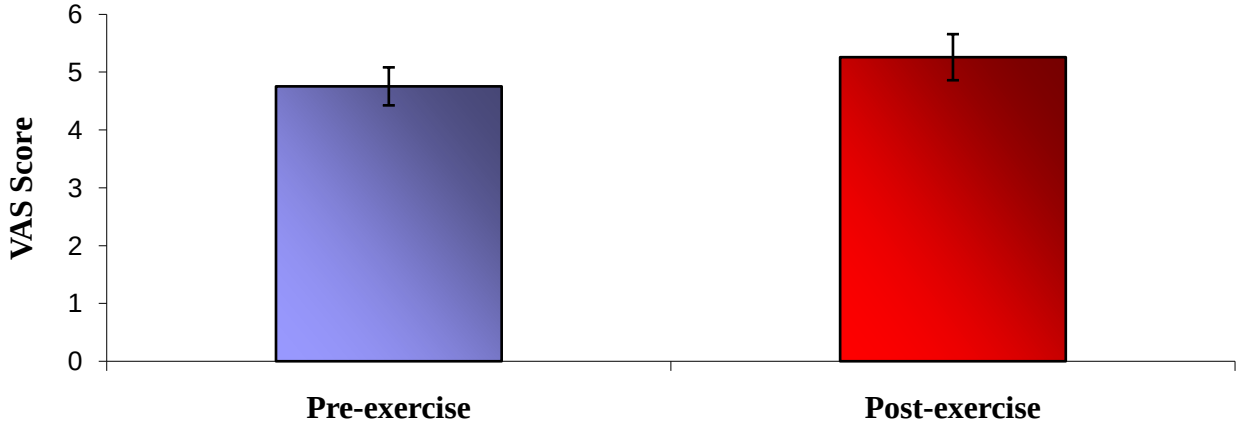
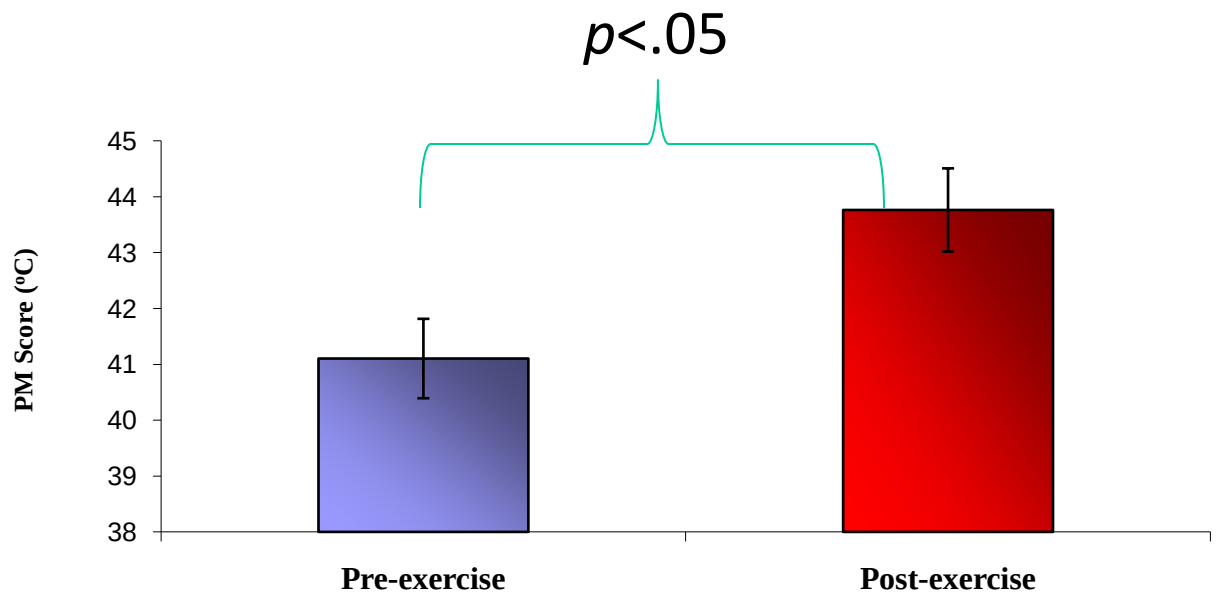
Pain Matching

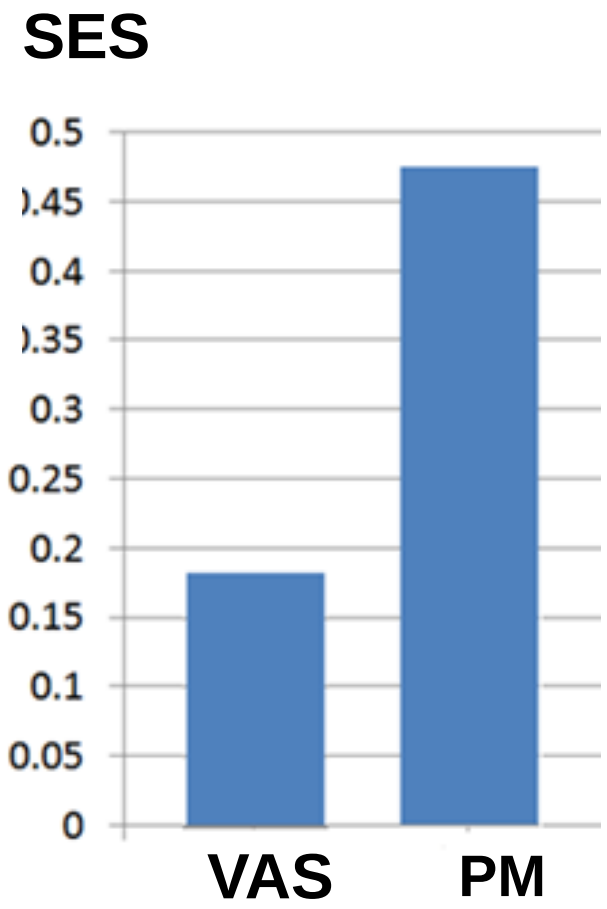
Subjects adjust thermode temp until $pain_{heat} = pain_{OA}$ (forced choice staircase procedure)

Delta Exercise Pain Results:

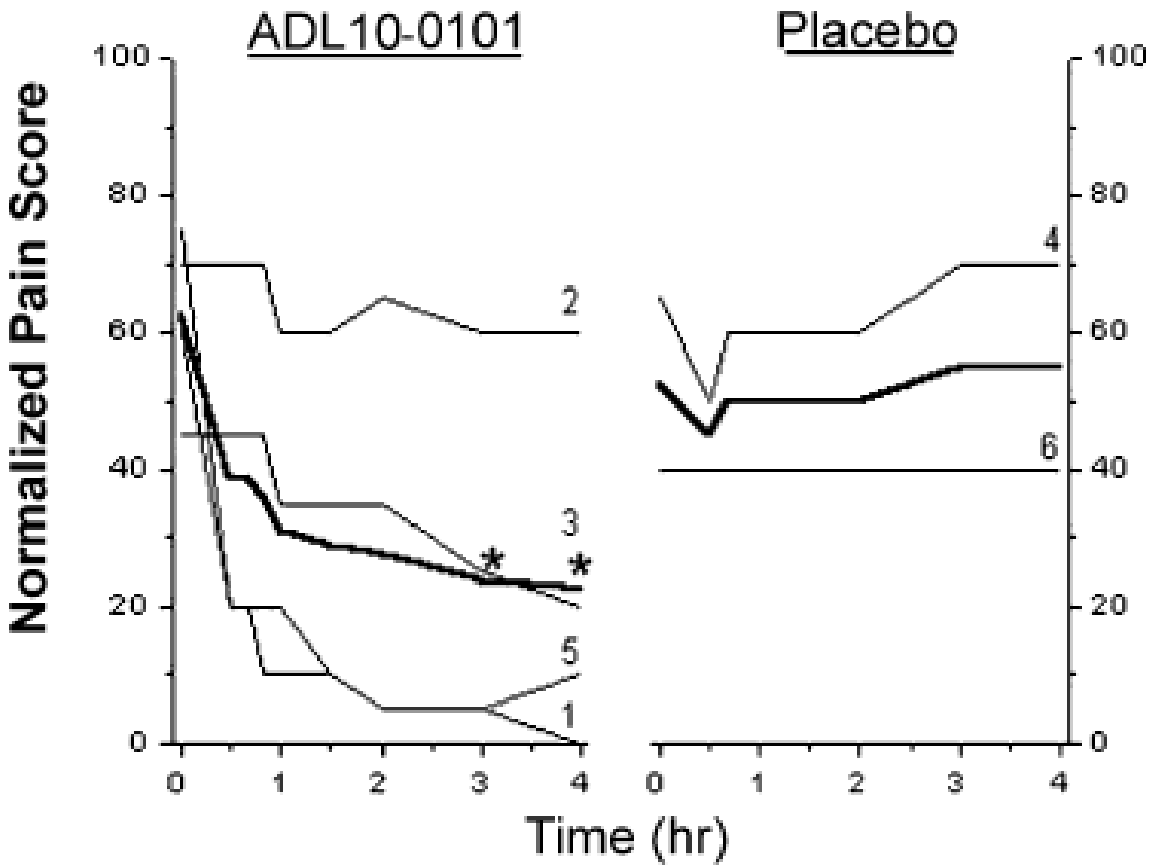
Change in pain significantly different for PM not VAS







Other explorations of alternative pain measures



P<.05

Eisenach J, et al, Pain, 2003

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Pain-Activity Composites

Actiwatch®-Score

Phillips-Respironics, Inc.

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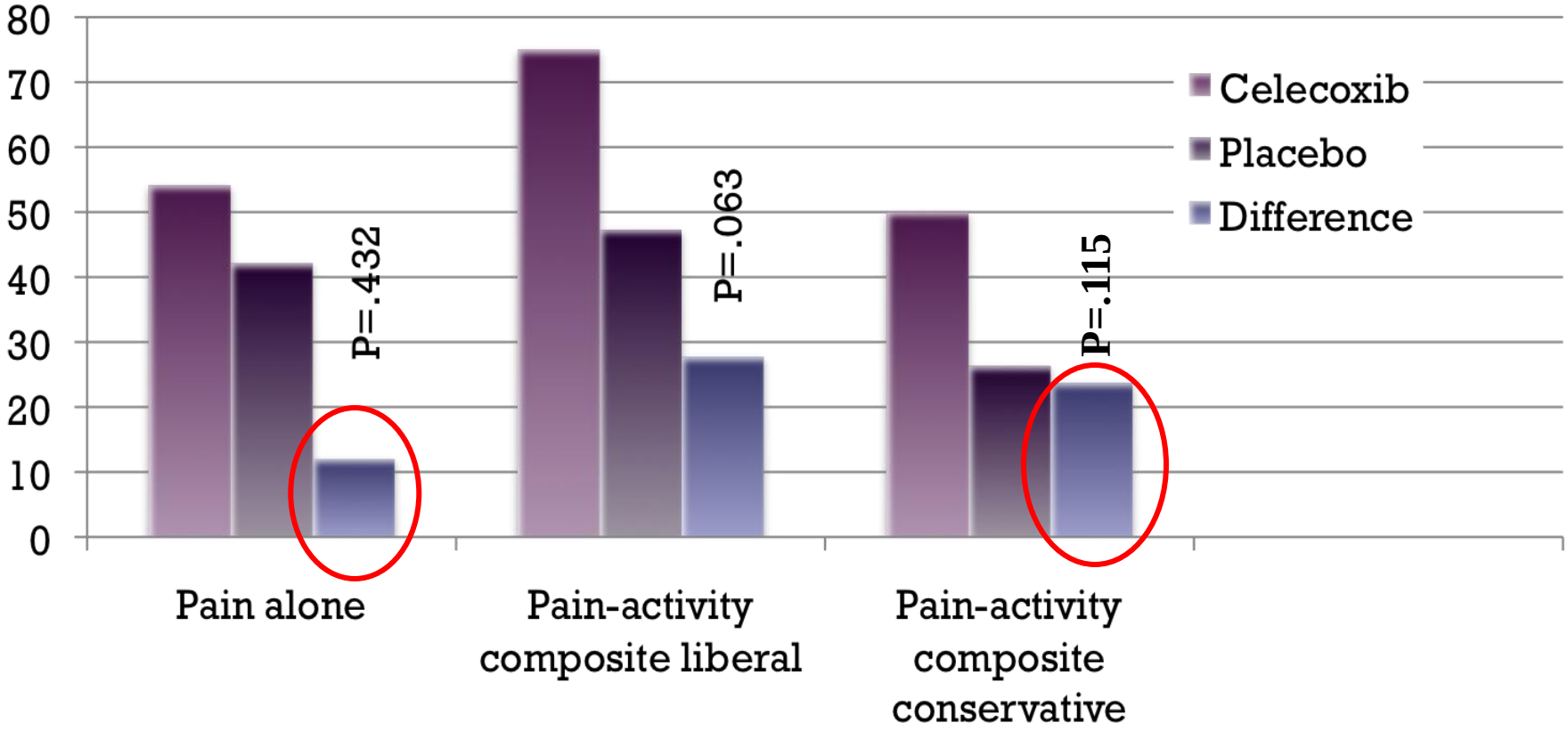
Pain-Activity Composites in an OA RCT, Celecoxib vs. Placebo, n=43



Pain alone: ≥20% improved from baseline; liberal: pain improved ≥20% OR activity improved ≥10%; conservative: pain pain improved ≥20% OR activity improved ≥10% WITHOUT deterioration in the other measure.

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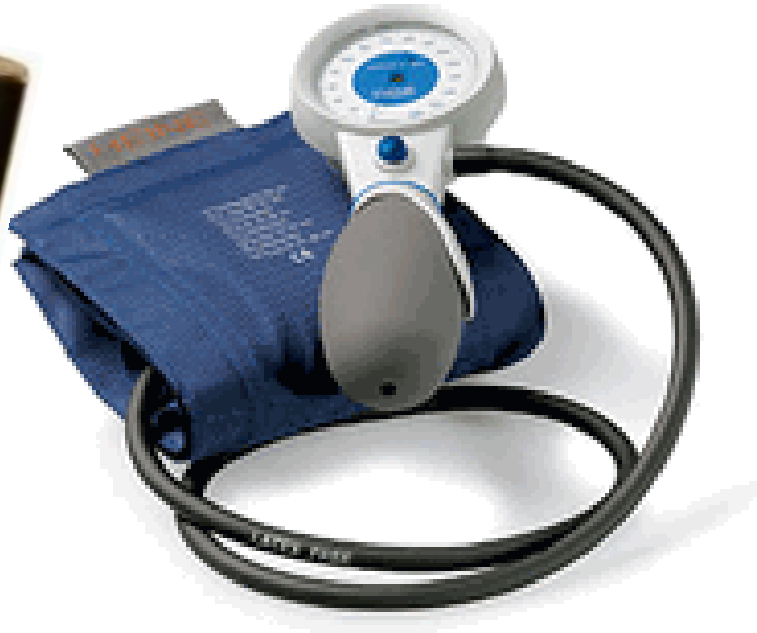
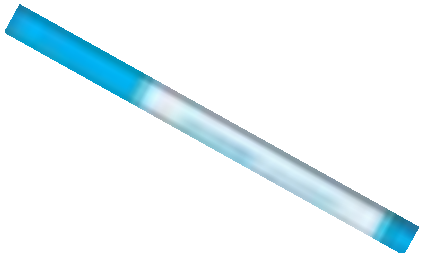
Bedside Sensory Testing Kit - OA





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Sensory Categories in OA: Pilot Study

	No hyperalgesia	1° hyperalgesia	2° hyperalgesia	1° and 2° hyperalgesia
Intact DNIC	N=3	N=1	N=2	N=2
Dysfunctional. DNIC	N=0	N=1	N=2	N=9

Alpha = .59 - .72

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Conclusions

- Meta-analytic methods can be used to shed light on the impact of methodologic factors on study outcome
- Experimental methods can be used to develop and test study design methods to increase assay sensitivity
- Success will require resources, perseverance, and patience: hitting home runs on the first swing is unlikely