ANALGESIC SOLUTIONS

Improving Assay Sensitivity in Analgesic Proof-of-Concept Studies

Nathaniel Katz, MD, MS
Analgesic Solutions, Inc.
Tufts University School of Medicine
IMMPACT, June 24-25, 2010

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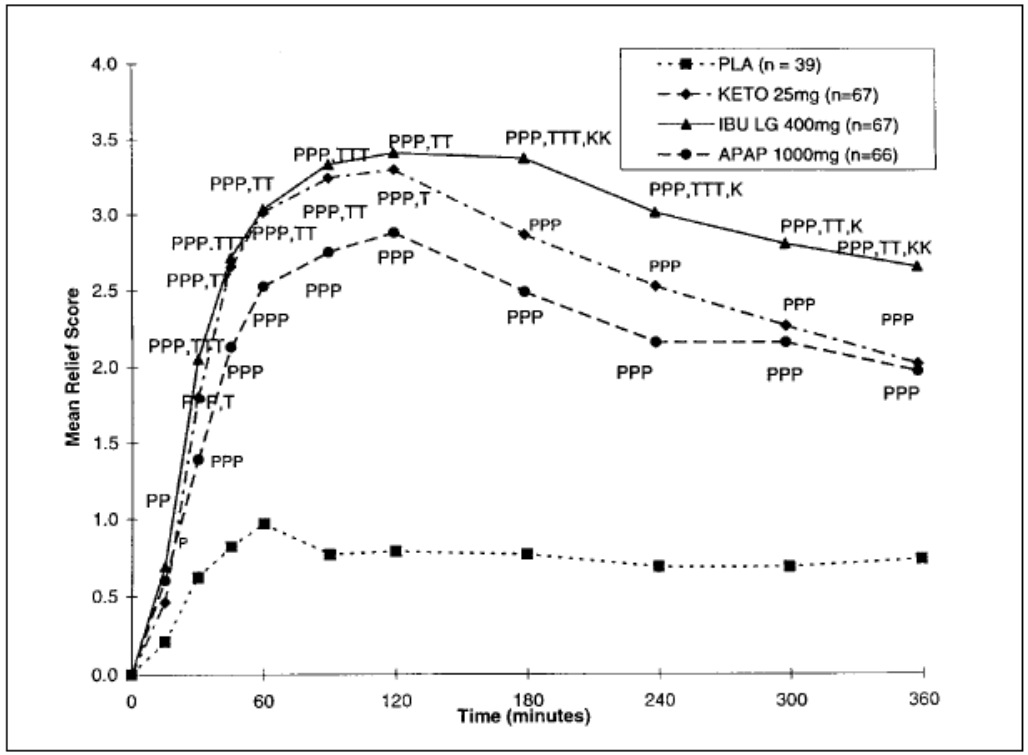
Part 1
Stories

Abraham Sunshine
January 3, 1928–January 2, 2007



Olson N, et al, J Clin Pharm, 2001

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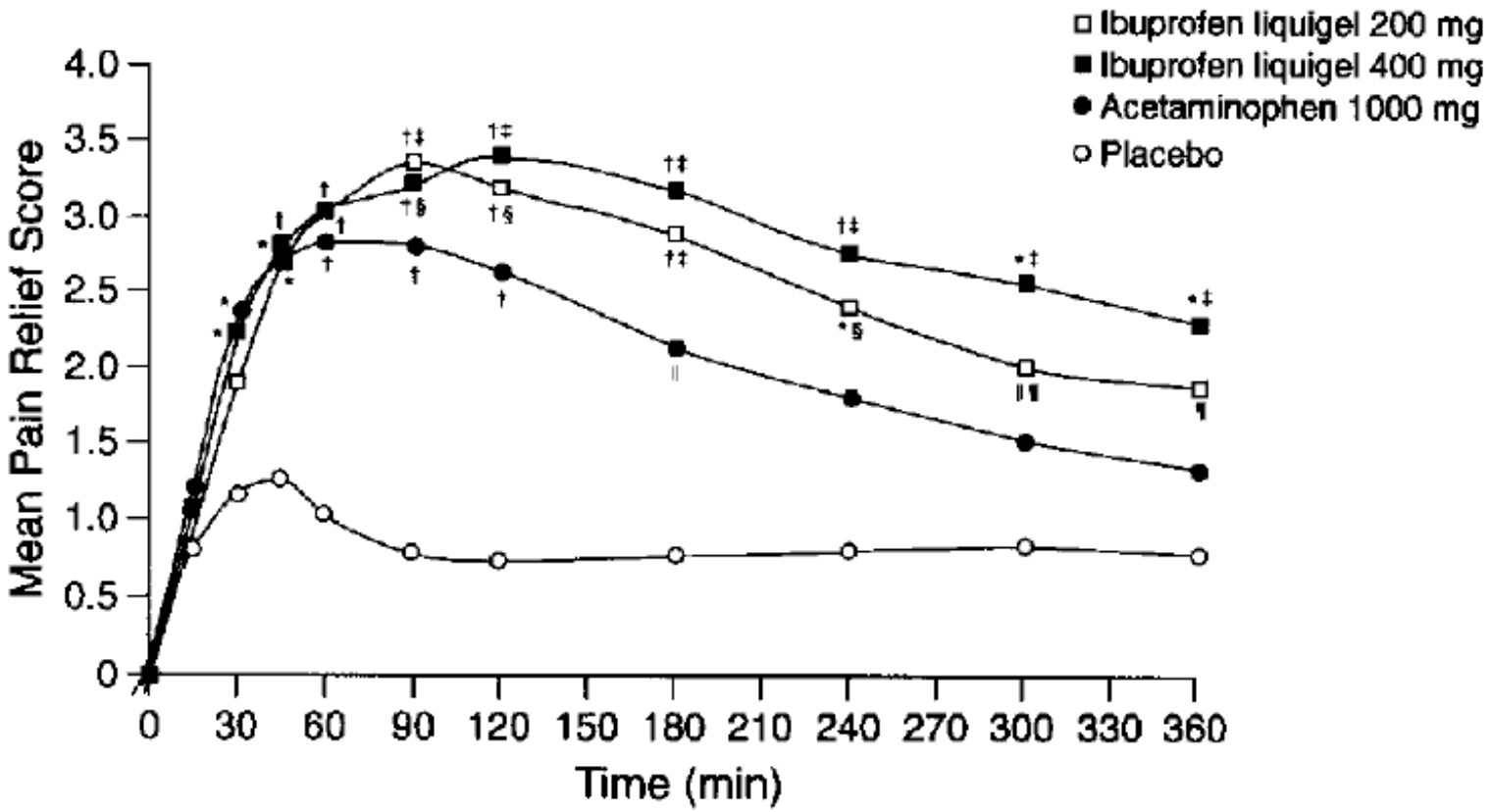

Hersh E, et al, Clin Ther, 2000

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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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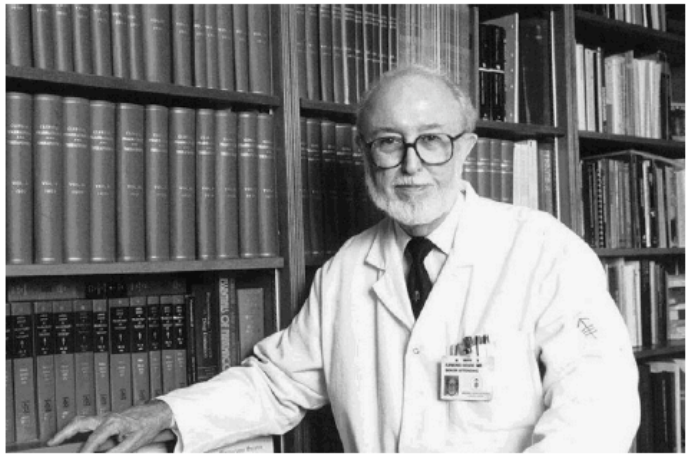
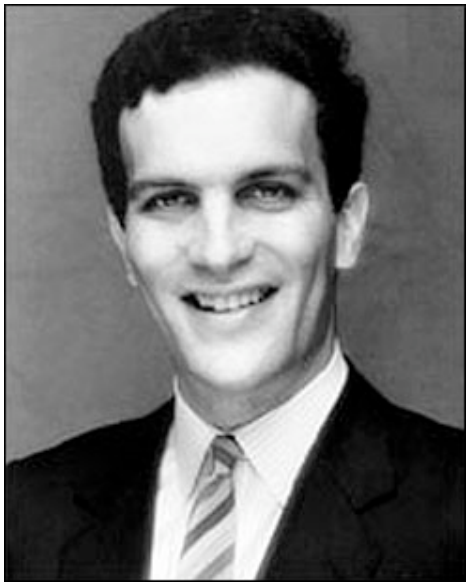
Ray Houde
(1916-2006)



Louis Lasagna
(1923-2003)

Mitchell B. Max
(1949-2008)



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Case Study – Assay Sensitivity (Inguinal Hernia Data)

	Lotus Research (n = 126)	All 24 Other Sites (n = 274)
Primary efficacy endpoint: mean difference between active and placebo (Δ)	0.81	0.56
Pooled standard deviation (SD)	2.25	2.56
Standardized effect size (Δ/SD)	0.360	0.219
N needed for 80% power at alpha = 0.05	244	658
Subjects enrolled per site per month (mean)	23.2	0.75
Overall Performance (time to 80% power)	10.5 months*	36.6 months **

***utilizing one site at Lotus** ****utilizing 17 non-Lotus sites in concert**

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Case Study – Assay Sensitivity (Surgical Hemorrhoidectomy)

	Lotus Research (n = 126)	All 24 Other Sites (n = 274)
Primary efficacy endpoint: mean difference between active and placebo (Δ)	55.9	32.6
Pooled standard deviation (SD)	192.93	205.46
Standardized effect size (Δ/SD)	0.29	0.159
N needed for 80% power at alpha = 0.05	376	1250
Subjects enrolled per site per month (mean)	14.2	.5
Overall Performance (time to 80% power)	26.5 months*	147 months**

***utilizing one site at Lotus** ****utilizing 17 non-Lotus sites in concert**

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Implication 1

- The effect size of a drug is not a fixed natural quantity, but is “elastic,” increasing or decreasing based on knowable features of study design and conduct.
- There is no “true” effect size of a drug, but only an “observed” effect size that is inseparable from the conduct of the experiment.

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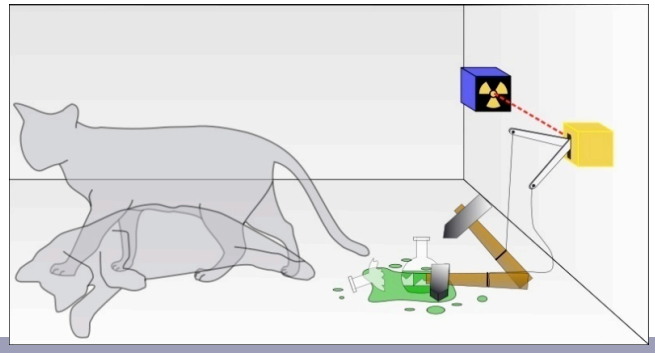
Standardized Effect Size

Heisenberg Uncertainty Principle

$$\Delta x \Delta p \geq \frac{\hbar}{2}$$

Schrodinger's Observer Effect



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Implication 2

- It should be possible to figure out what factors amplify observed effect sizes, and implement them in studies, resulting in “effect size amplification,” or improved assay sensitivity
- The consequence of effect size amplification would be reduction in sample size requirements to discriminate treatment conditions, or reduced likelihood of trial failure

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Paradigm Shift

Old paradigm

- Drugs have a **fixed** "true" effect size
- Individual trials show variable results due to "random noise"
- Goal is to find "true" effect size by conducting "large" studies or meta-analyzing multiple studies

New paradigm

- **Observed** effect size based on inseparable drug-experiment dyad
- Variable results predictable based on design/conduct
- Goal is to conduct studies with high sensitivity and specificity

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Part 2
Evidence

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Do knowable factors impact observed effect sizes of drugs (assay sensitivity)?

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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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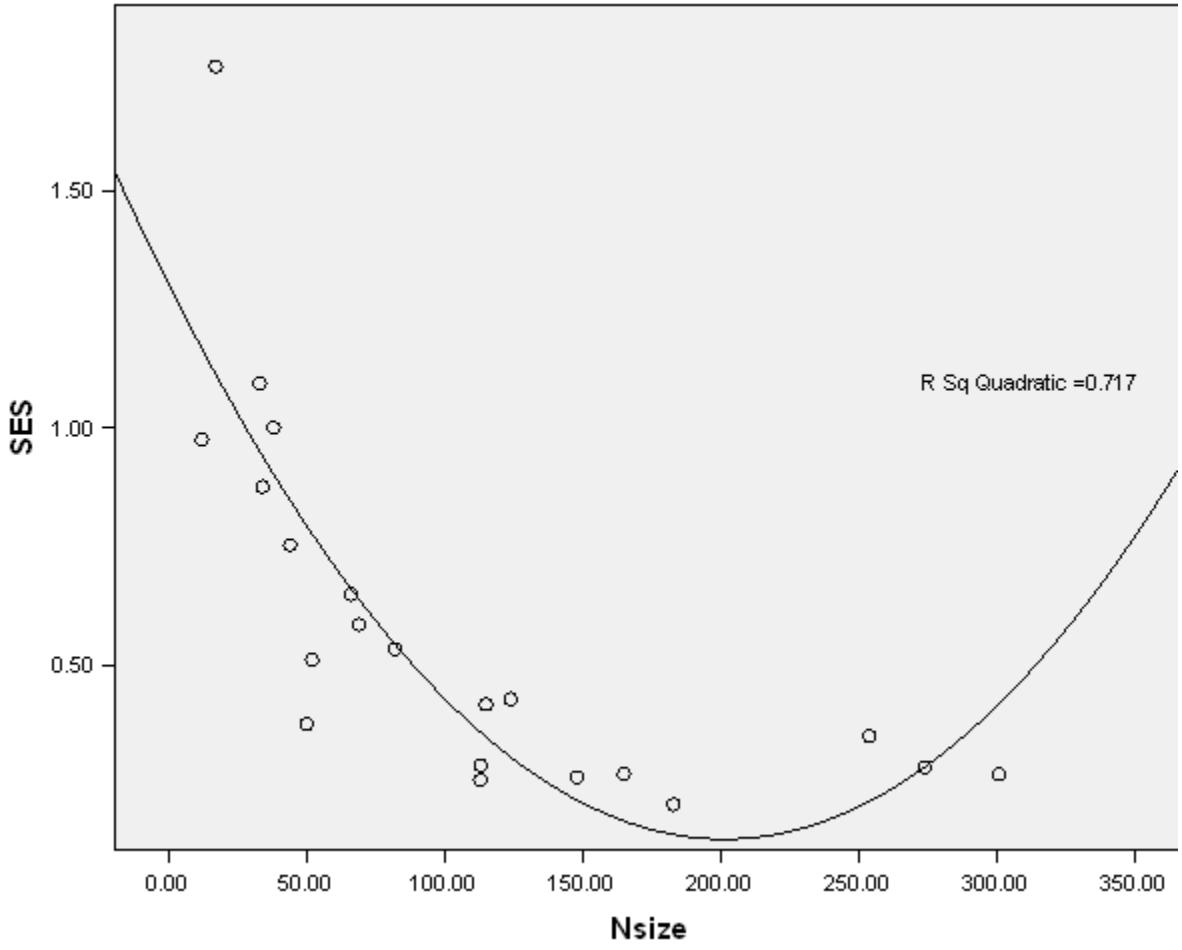
Standardized effect size vs. sample size in opioid studies



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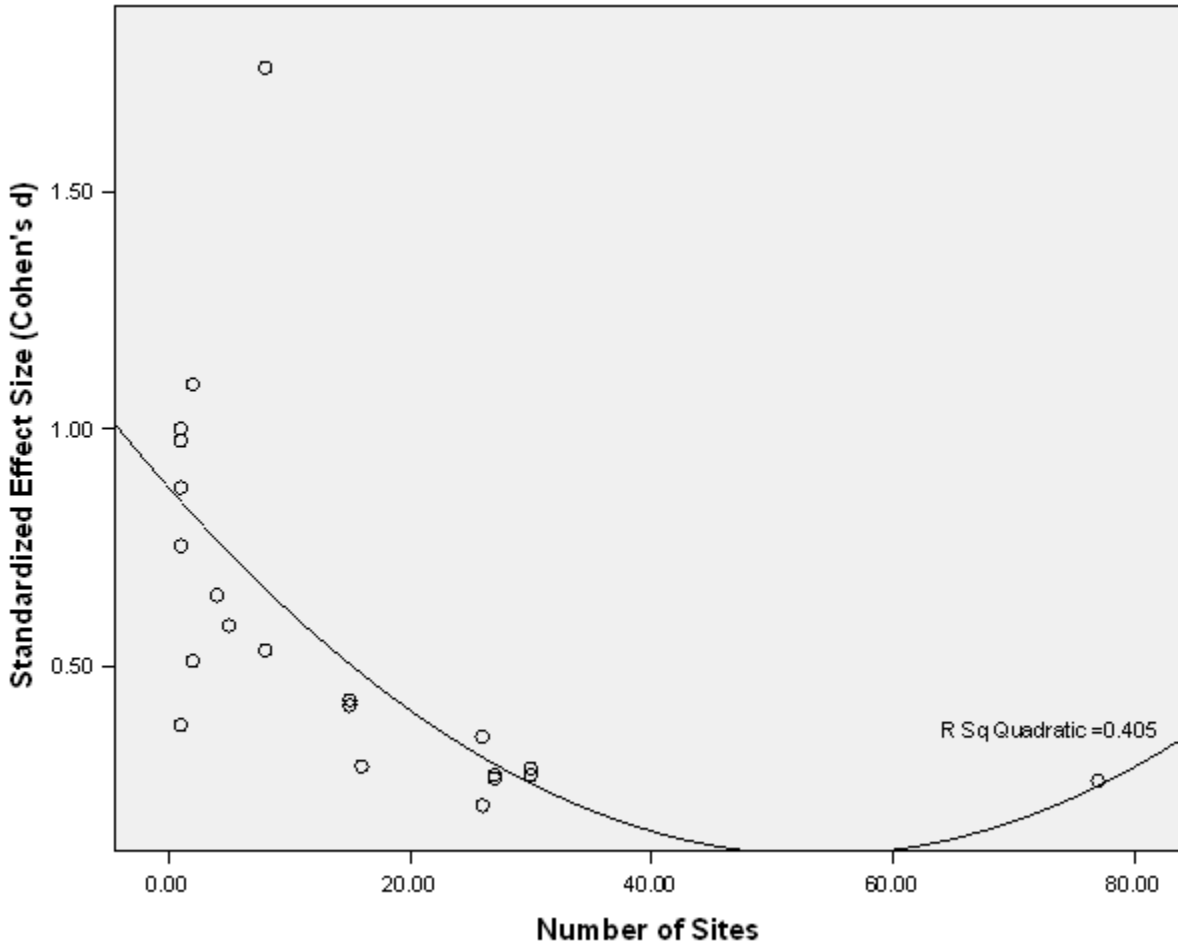
Standardized effect size vs. number of sites, opioid trials



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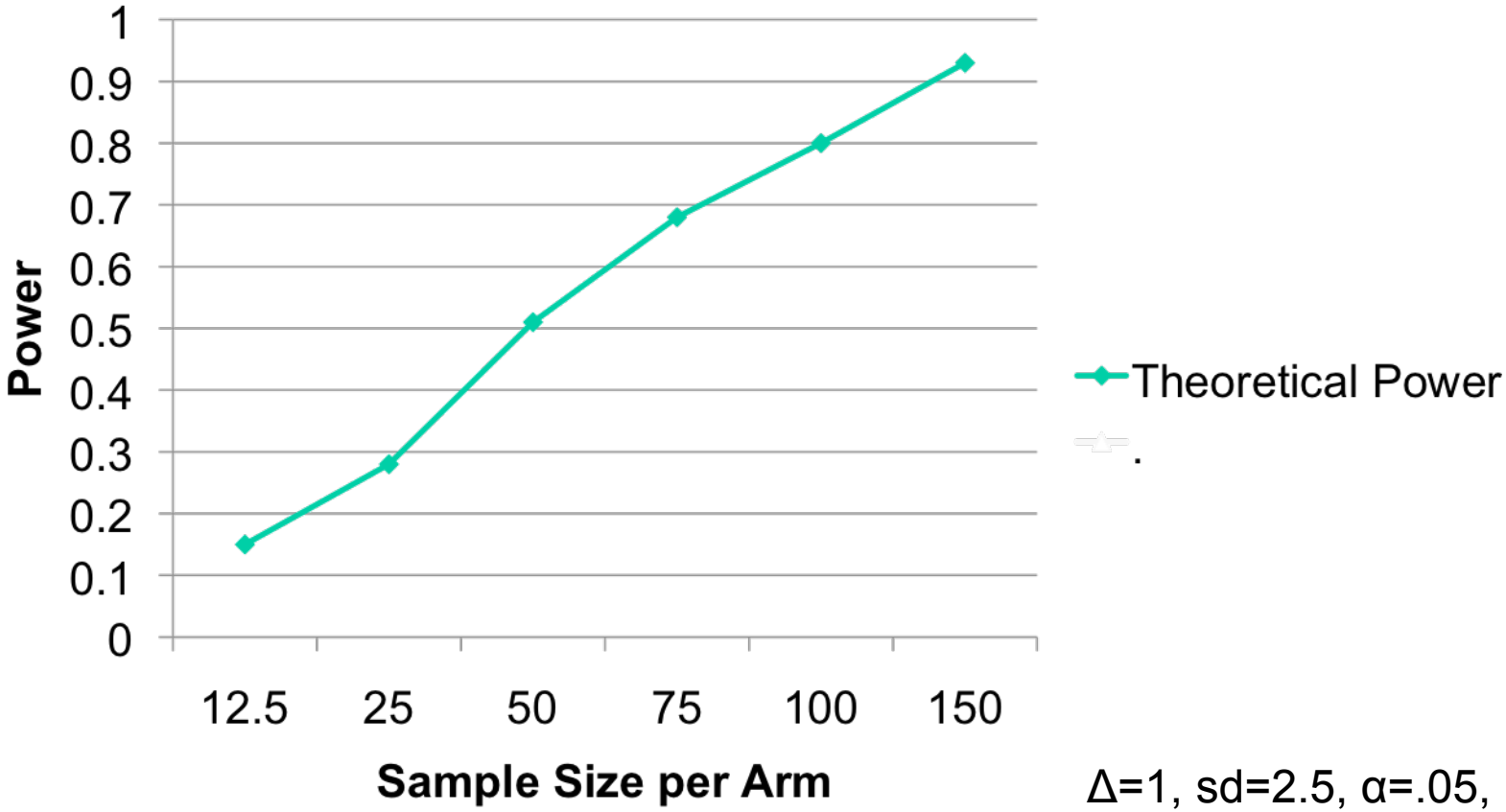
True vs. Actual Power



Δ=1, sd=2.5, α=.05, power=.8

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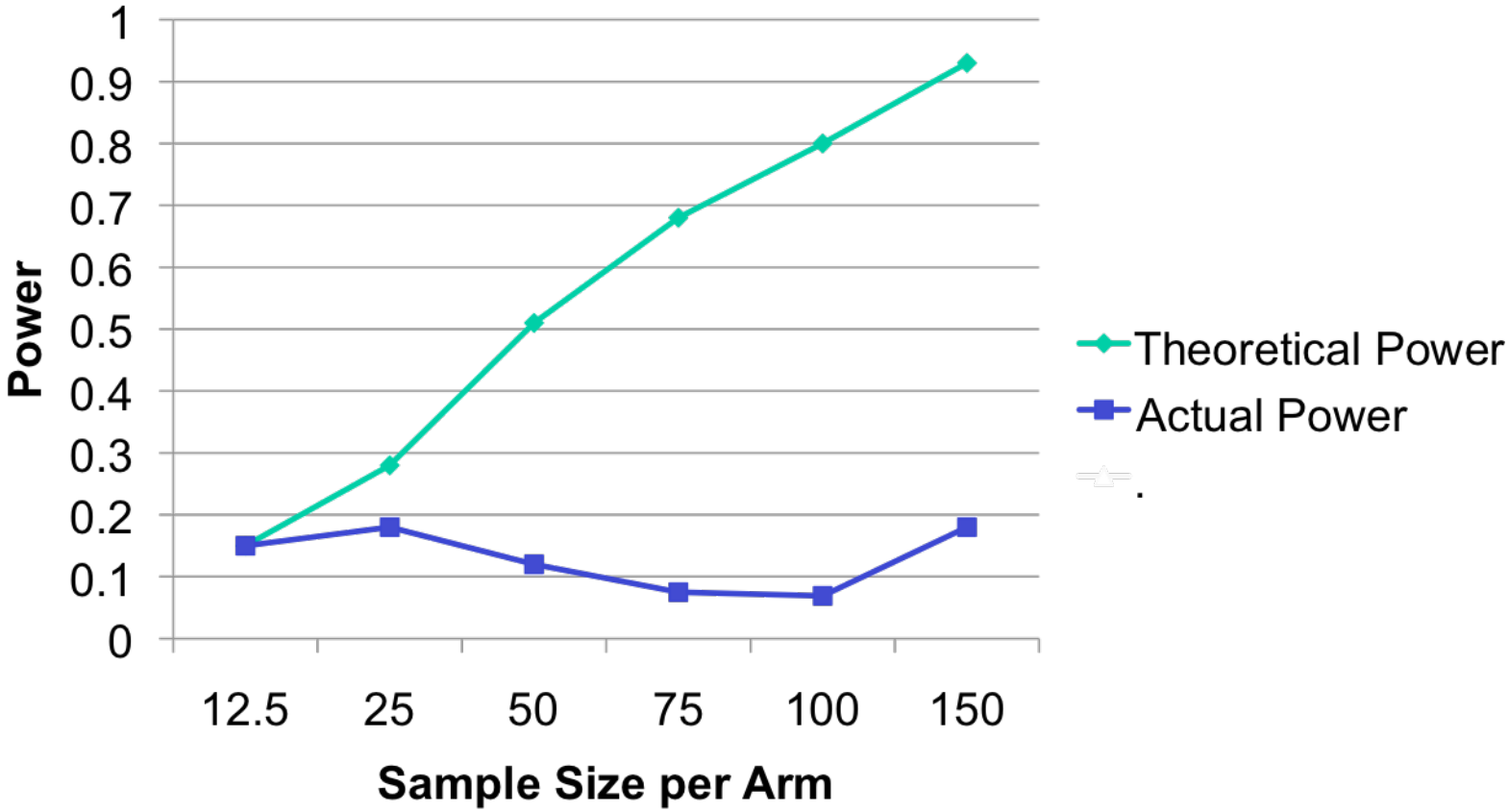
True vs. Actual Power



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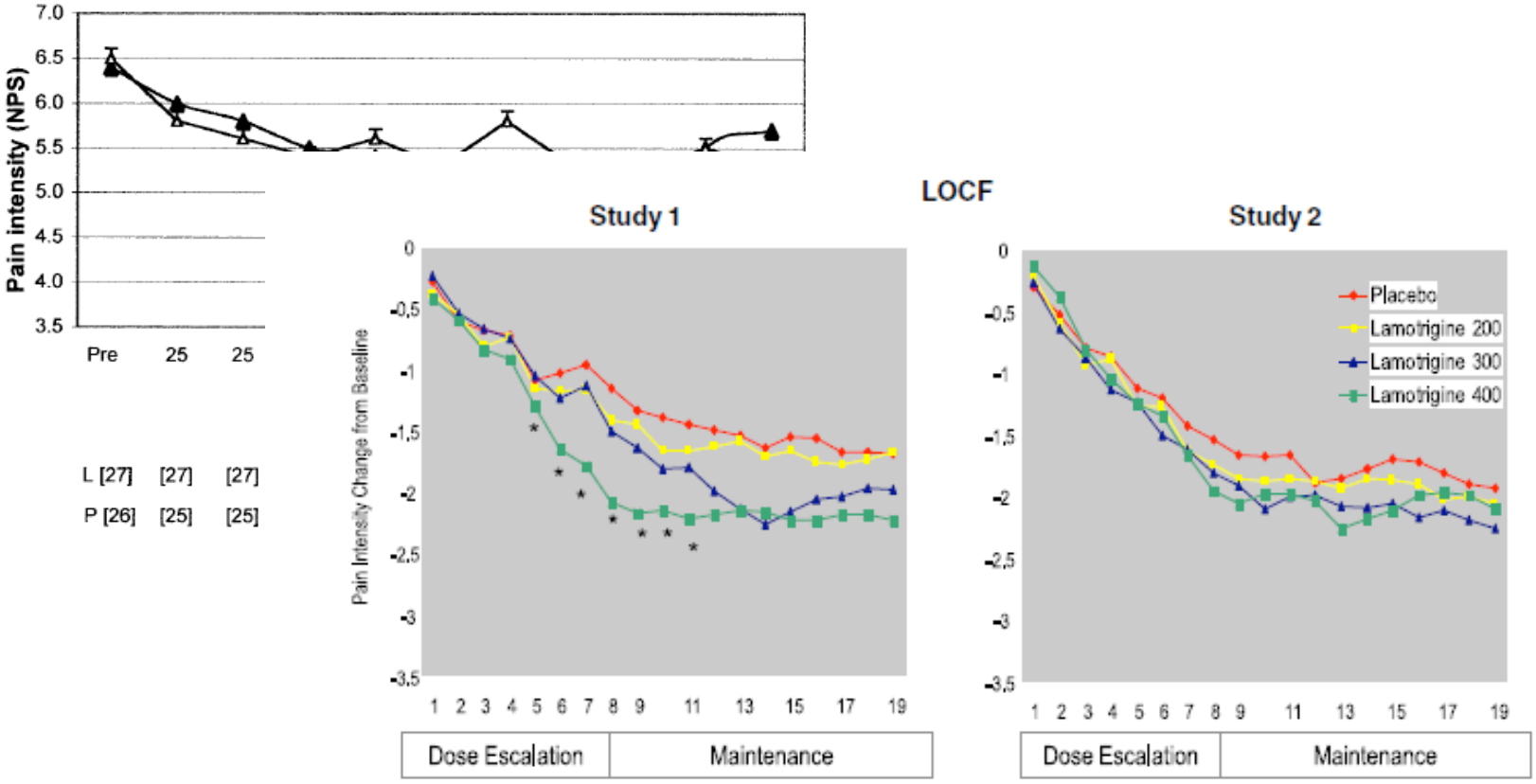
Lamotrigine in PDN



Eisenberg E, et al, Neurology, 2001; Vinik A, et al, J Pain Sympt Manage, 2007

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Failure: Neuropathic Pain Trials

	Positive	Negative	P-value
Placebo response	15.8	26.3	0.002
Year (pub)	1995.2	1998.5	0.047
PHN	16	4	
Polyneuropathy	39	12	
Study design			0.006

Katz J, Neurology, 2008

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Failure: PDN Studies

Correlation between design feature and SES

- Longer duration of PDN (r = 0.80)
- Shorter treatment duration (r = 0.65)
  - Probably a proxy for earlier capture of primary endpoint
- Shorter titration (r = 060)
  - Probably a proxy for shorter trials
- Smaller sample size (r = 0.55)
  - Probably a proxy for fewer sites
- Fewer sites (r = 0.50)
- Fewer study visits per trial duration (r = 0.44)
  - May be due to less “nurturing nurse” effect or potentially higher dropouts
- Two arms (SES = 0.60) vs. >2 arms (SES = 0.40)
- No rescue medication (SES = 0.60) vs. rescue medication (SES = 0.40)

Dworkin R, Katz N, et al, unpublished

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Conclusions

- Specific trial features DO have a robust impact on observed effect sizes
- More data are needed on what these factors are and what their impacts are
- Investigators can use an “evidence-based trial design” approach to amplify effect sizes and therefore decrease sample size requirements

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Evidence-based trial design

The use of systematic and quantitative examination of the impact of clinical trial features on assay sensitivity to inform the design of new clinical trials

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Part 3
Explorations

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Are there specific aspects of clinical trial design that can be improved, with consequent improvement in assay sensitivity?

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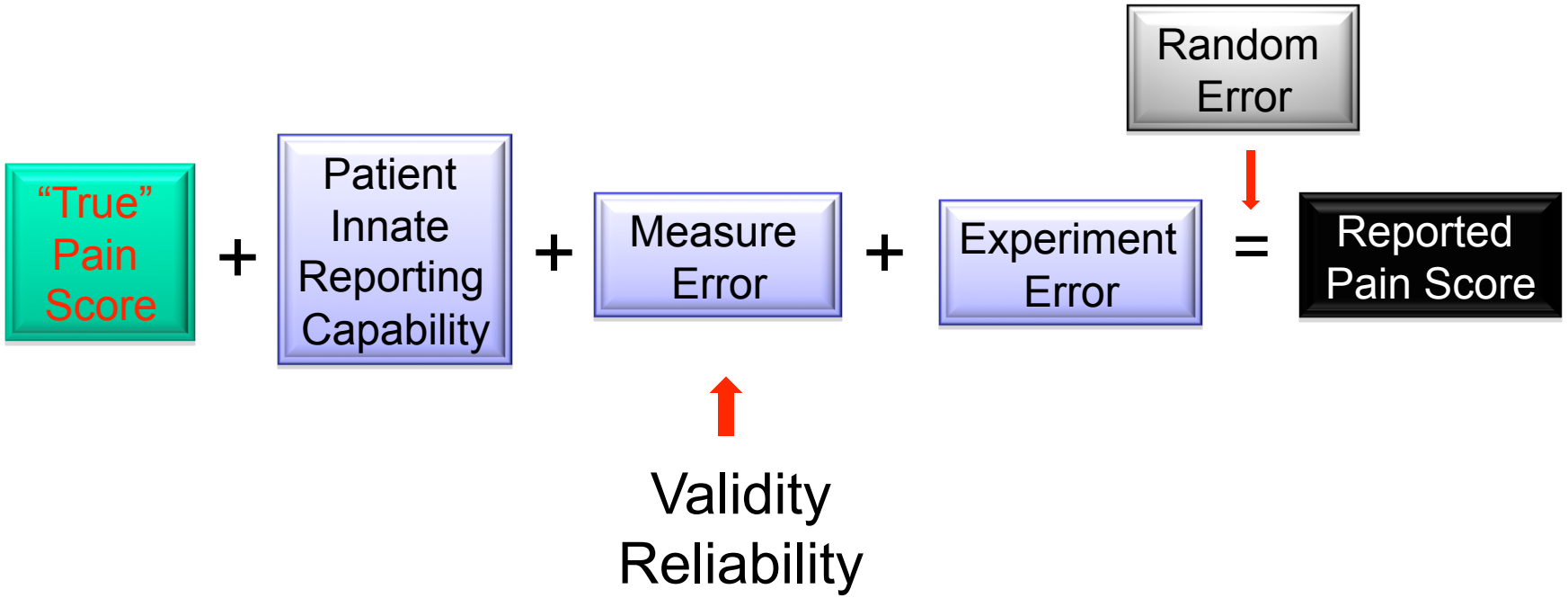
Improving pain measurement

What generates a pain score?



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Patient Innate Reporting Capability

Identifying “accurate” pain reporters:

The Comprehensive Screening Algorithm Study

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Objectives

- To develop a method for rating how accurately an individual patient reports pain (“good pain reporters”)
- To determine whether patients with OA differ in pain reporting accuracy
- To determine whether predicted pain reporting accuracy relates to accuracy in reporting clinical pain

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Psychological Assessment (Ψ)

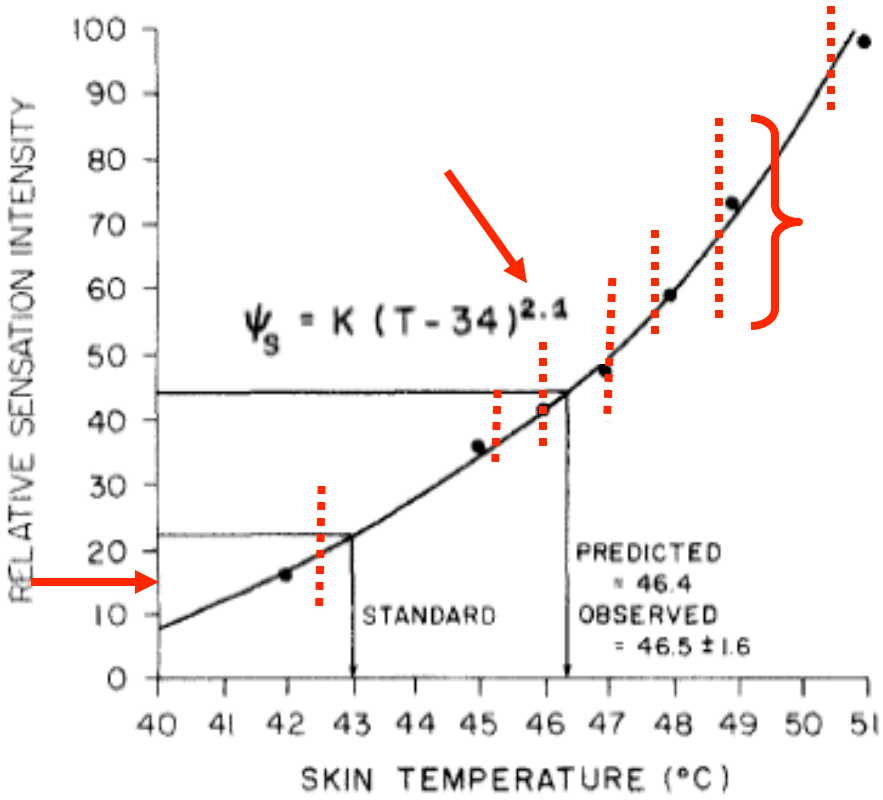
Neuropsychological battery – measures psychological constructs hypothesized to influence pain reporting:

- Depression (CES-D)
- Anxiety (STAI)
- Neuroticism (EPQ-A)
- Somatization (PHQ-15)
- Catastrophizing (PCS)
- Hypervigilance (KRS)
- Fear of Pain (FPQ)
- Pain Attitudes (PAQ-R)
- Expectation of pain relief (HG)
- Hopefulness for pain relief (HG)
- Quality of life (NHP)
- Social desirability (M-C SDS)
- Locus of control (LCS)

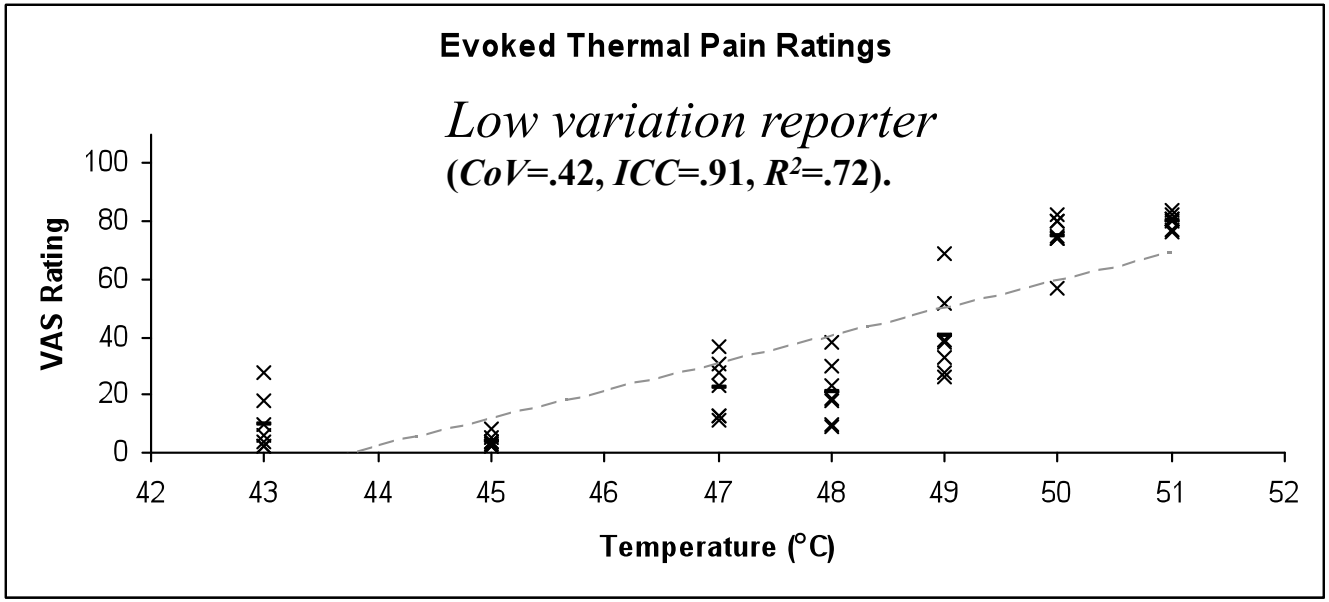
Psychophysical Assessment(Φ)

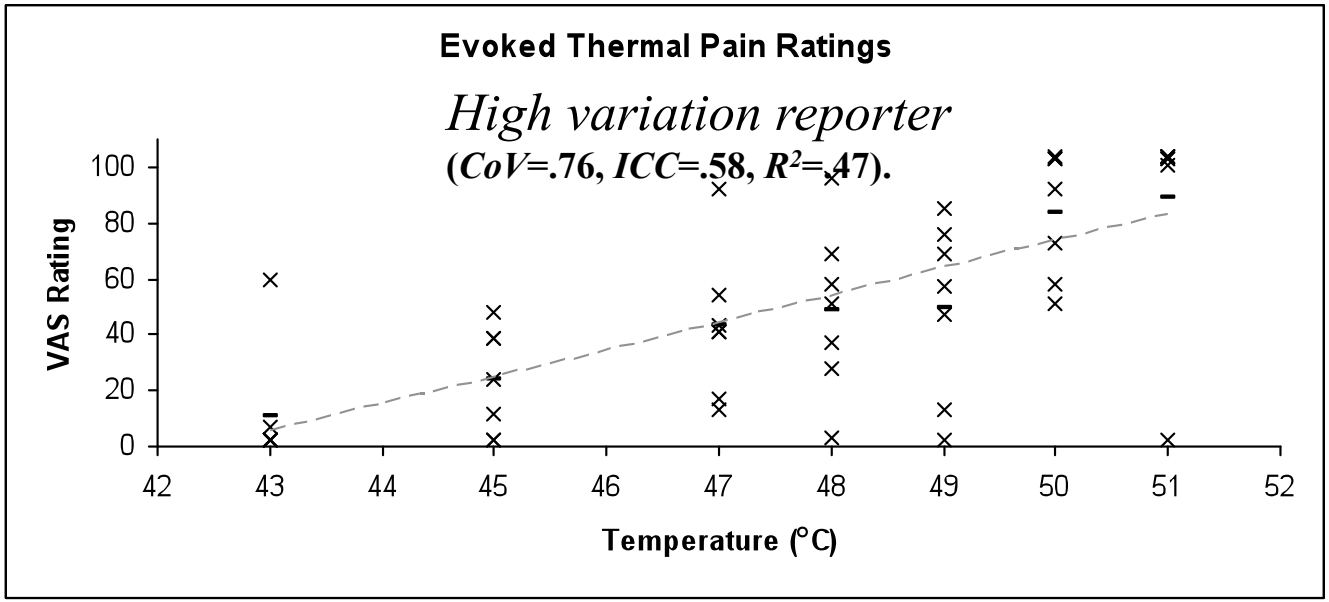
I. *Experimental Pain Rating*

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



Psychophysical Profile Samples Φ





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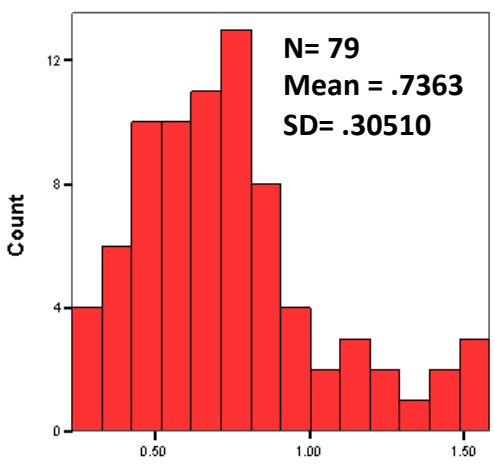
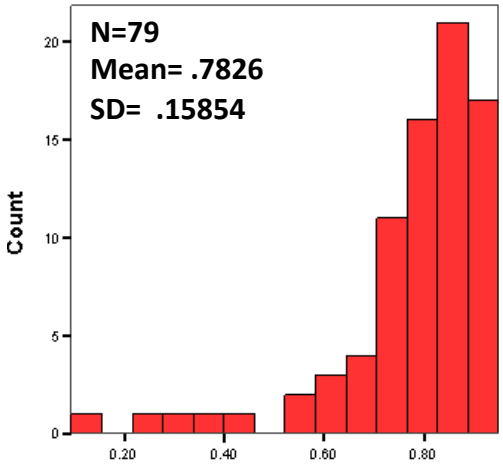
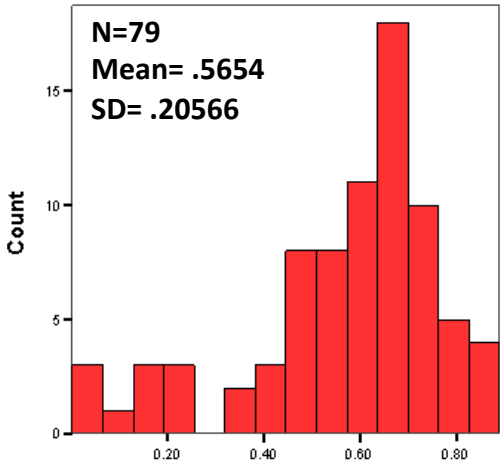
Frequency Plots for Pain Reporting Skill



CoV



ICC



R^2

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

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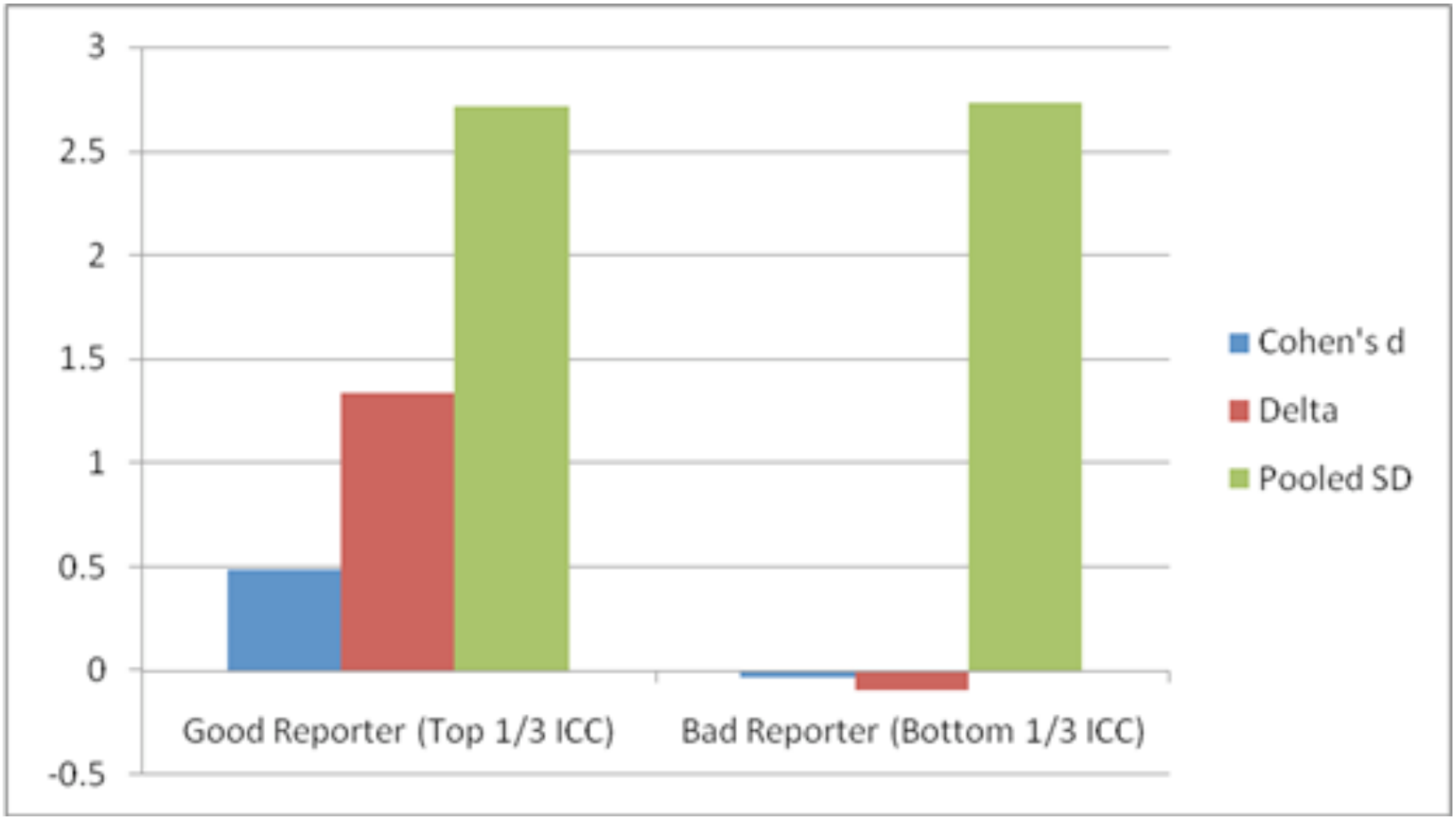
Pre- vs. post-exercise VAS scores in “good” vs. “bad” pain reporters



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Conclusions

- People differ in how accurately they report experimental pain
- This can be measured
- Poor reporters of experimental pain also poorly discriminate pre- vs. post-exercise OA pain
- Poor pain reporters may also be bad at discriminating analgesics from placebo

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Measure Error

Finding more responsive pain measures:

Pain Matching

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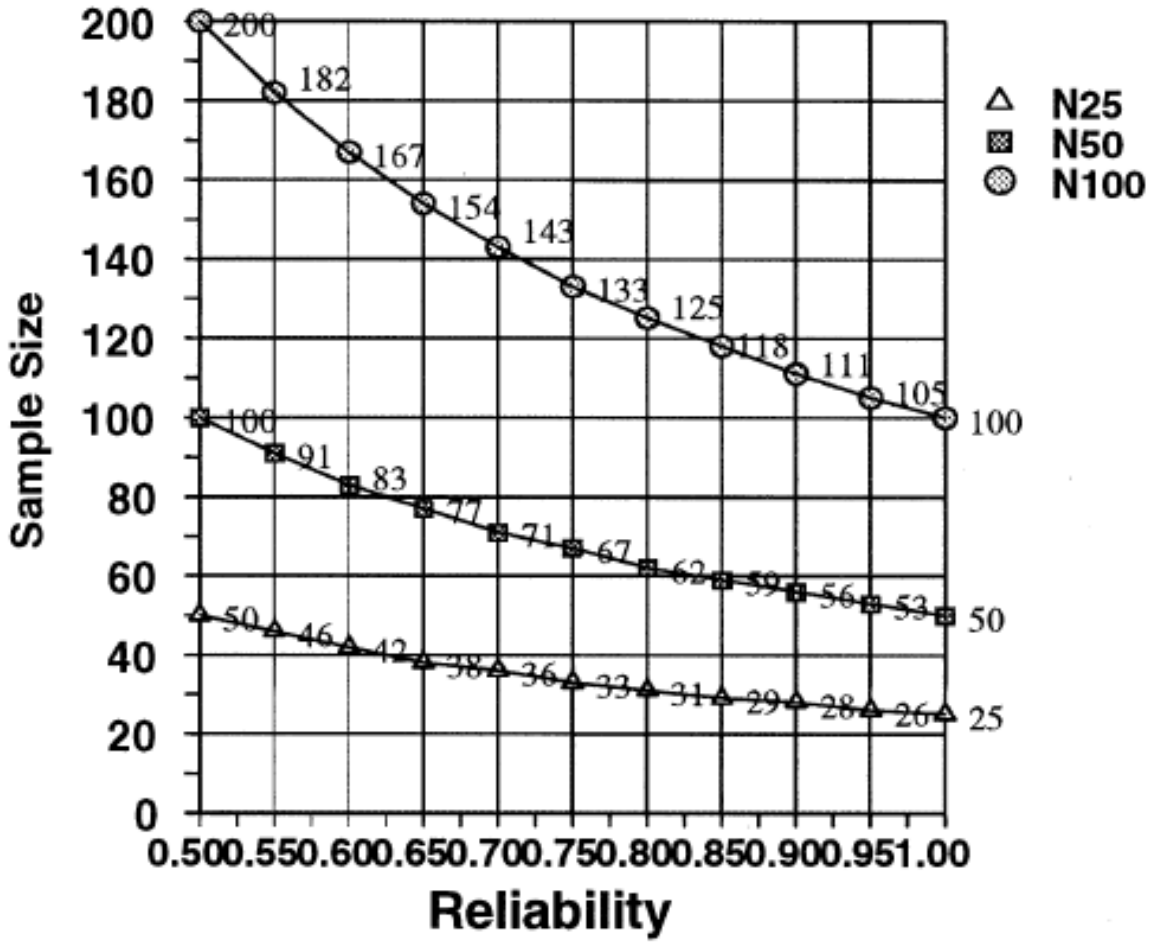
Reliability: Improved reliability decreases N requirements



Perkins DO, et al, Biol Psych, 2000

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Validity: Discordance between VAS and gold standard pain measure

Less than 50% agreement between pre-post change in VAS compared to "gold standard" interview in knee OA study

	Questionnaire			
Interview	**Better**	**No change**	**Worse**	**Total**
Pain scores				
Better	6	1	2	9
No change	7	2	1	10
Worse	1	0	0	1
Total	14	3	3	20*

Campbell R, BMJ, 2003

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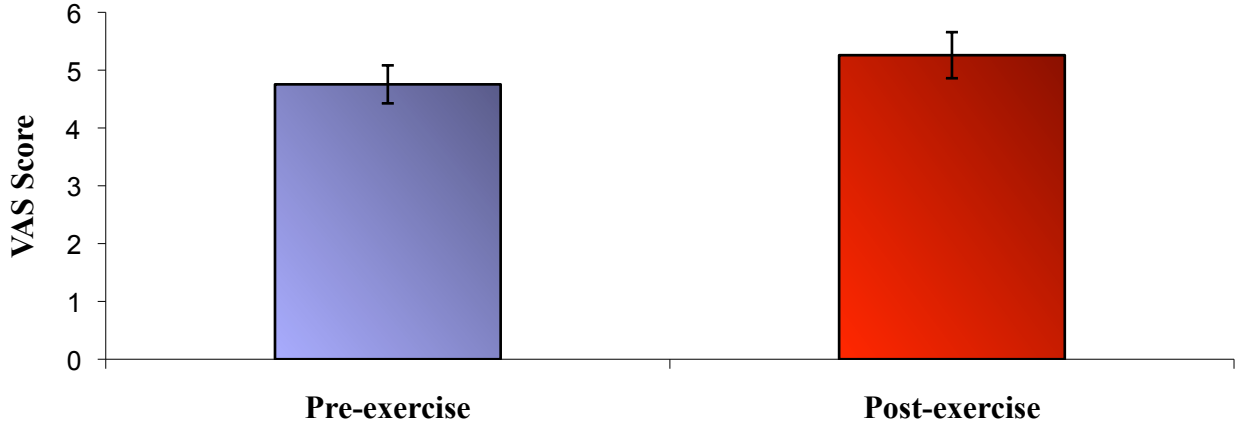
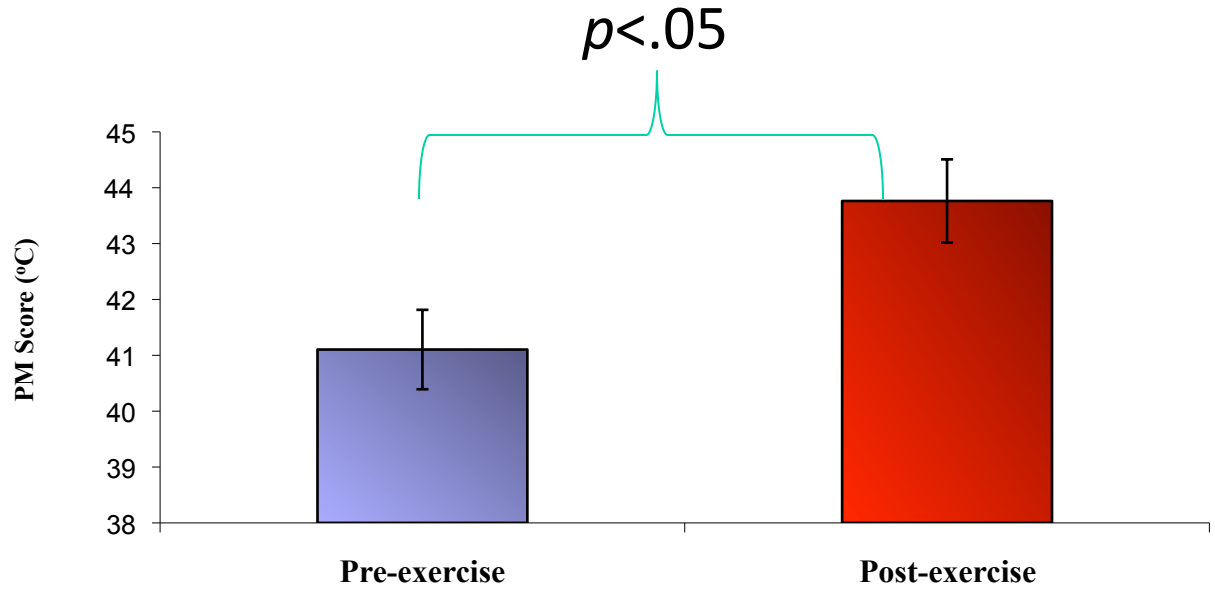
Pain Matching

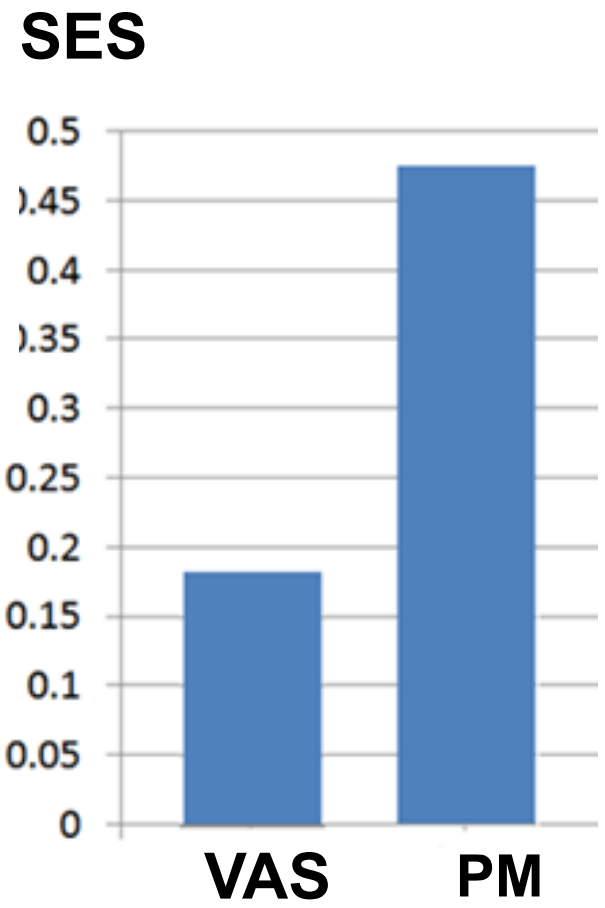
Subjects adjust thermode temp until $pain_{heat}$ = $pain_{OA}$ (forced choice staircase procedure)

Delta Exercise Pain Results:

Change in pain significantly different for PM not VAS







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Validity of VAS vs. PM

		VAS Worse		PM Worse		
		Yes	No	Yes	No	
PGIC Worse	Yes	14	8	17	5	22
	No	9	12	14	7	21
		23	20	31	12	43
% concordant with PGIC worse		VAS	64%		PM	77%

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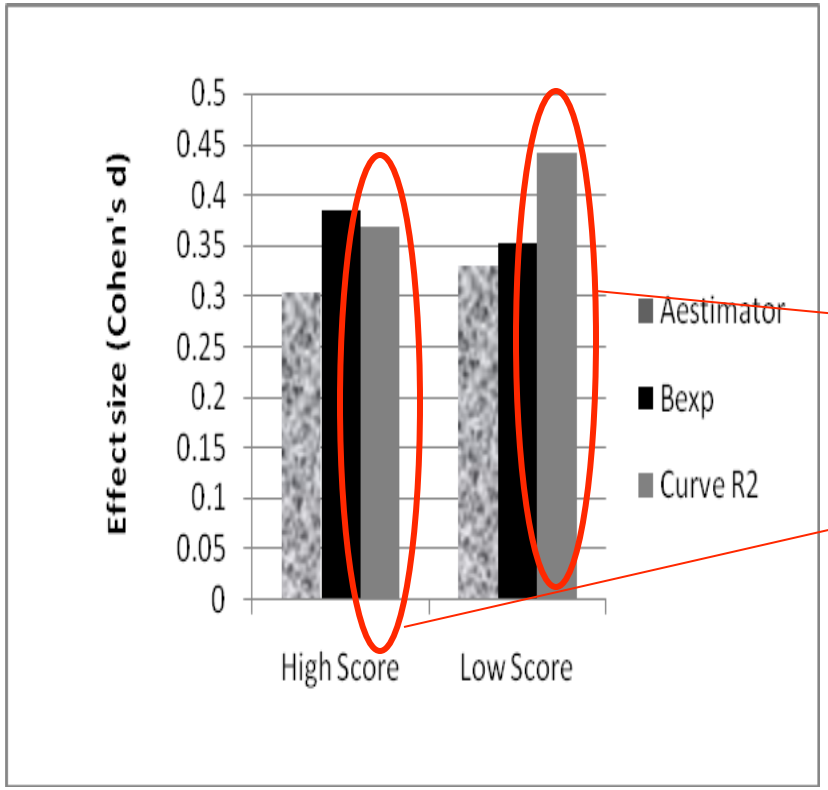
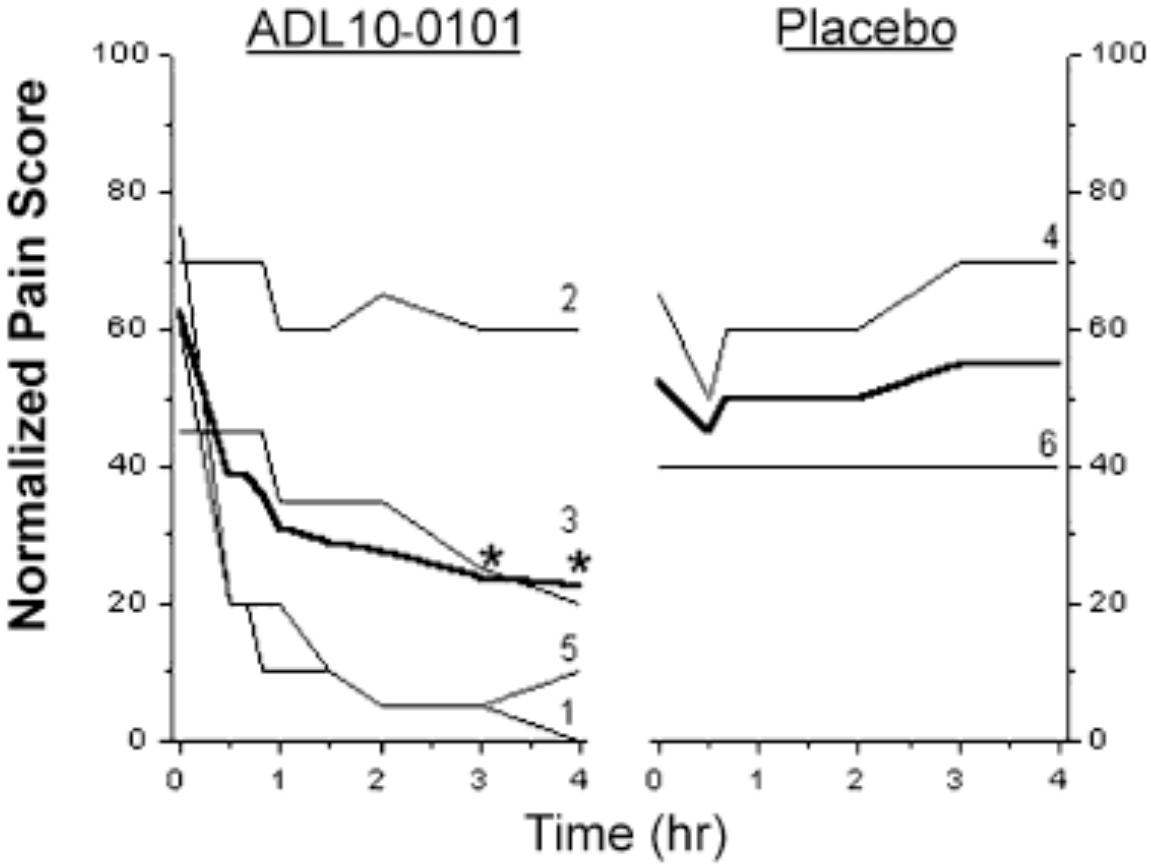
Pain Matching improves pain reporting in “bad pain reporters”



Using Pain Matching, “bad pain reporters” become nearly as good as “good pain reporters” on reporting clinical OA pain.

Other explorations of alternative pain measures



P<.05

Eisenach J, et al, Pain, 2003

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Conclusions

- The VAS performed poorly in distinguishing pre- vs. post-exercise pain in our OA study
- While the fact of "validity" of VAS is established, the degree of validity is suspect
- PM was a more responsive measure than VAS and improved performance of "bad reporters"
- More responsive measures of pain than VAS can and should be developed

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Measure Error

Pain-activity composites as more valid and responsive measures of analgesic effect:

The “Actiwatch” Study

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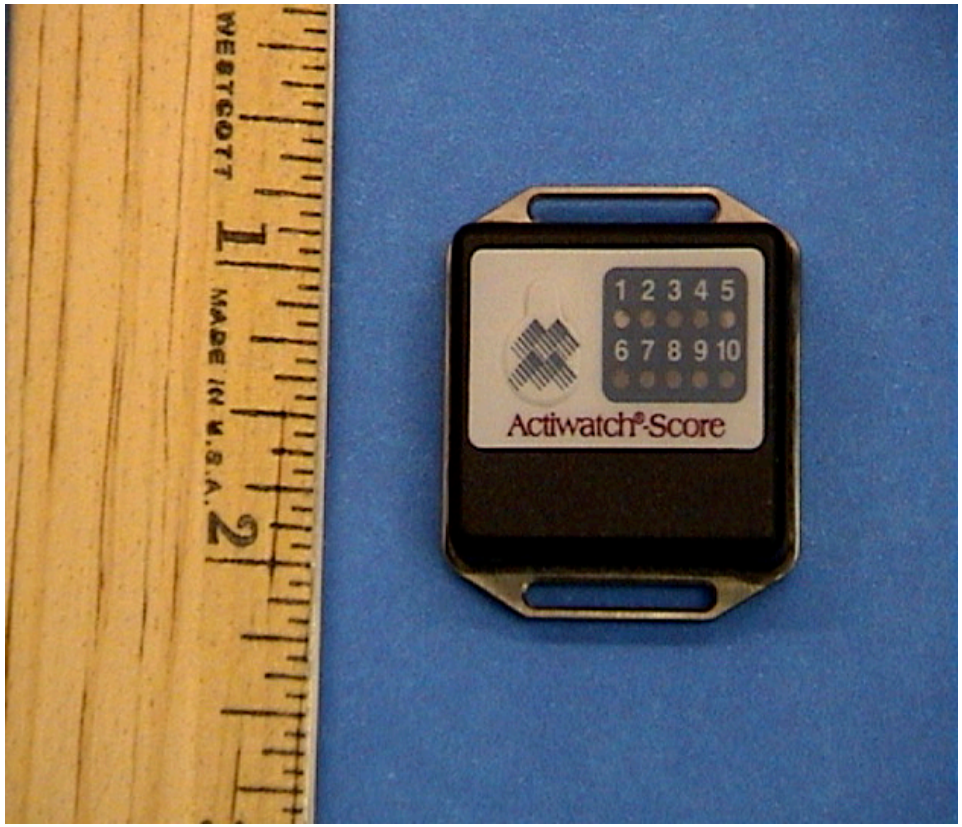
Pain-Activity Composites



Actiwatch®-Score

Phillips-Respironics, Inc.

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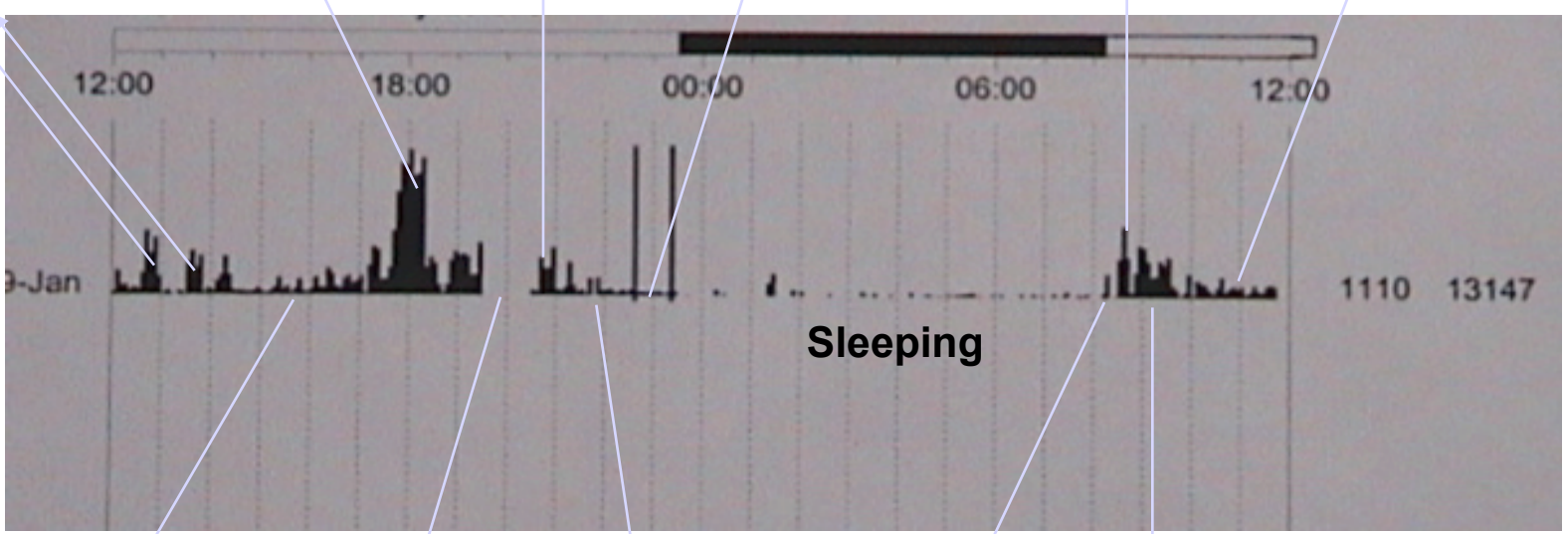
Actogram



Walking

Running

Preparing dinner

In bed; reading

Getting ready

Office work-desk

Sleeping

Office work-desk

Swimming

Couch sitting; reading

Got up

Walking

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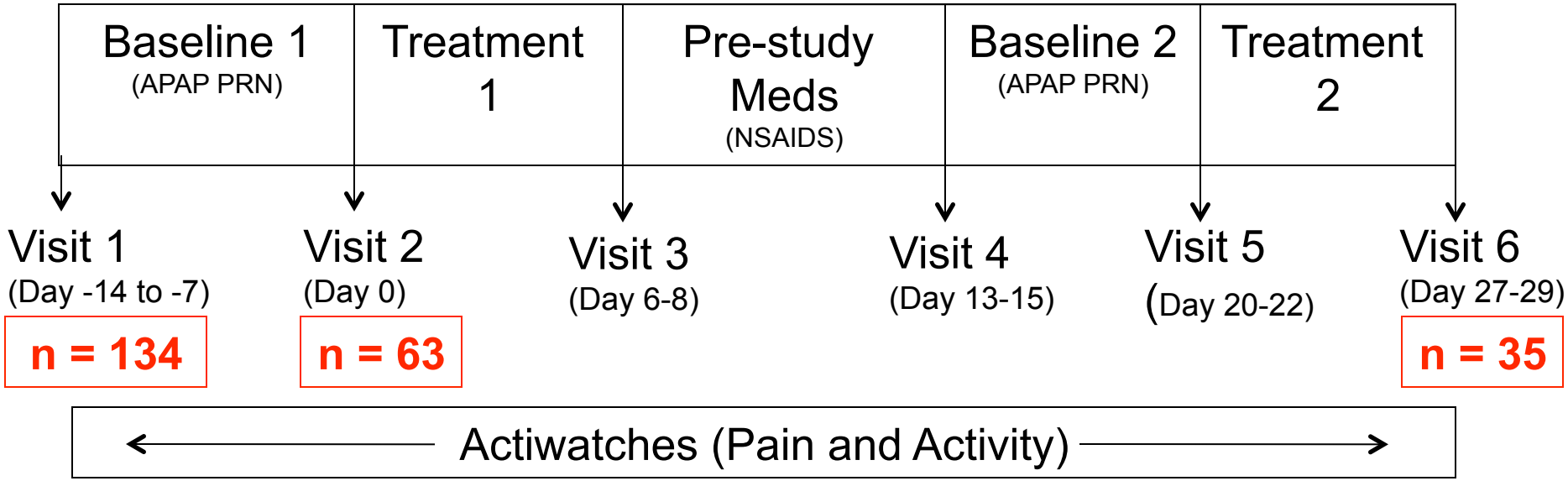
Actiwatch®
Cross-Over Study Design



Primary Objective:
To determine whether a composite measure of pain (Actiwatch® QID pain scores) and activity (actigraphy) is a more responsive measure of analgesic effect (celecoxib – placebo) than either component alone.

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Pain Measures: Celecoxib vs. Placebo (Difference from Baseline - ITT Population)

Variable	[N]	Mean Delta* (SD)	*p-value*
In Clinic Pain Score (24 hr)	47	0.9 (2.73)	**0.023**
In Clinic Pain Score (week)	47	1.0 (2.65)	**0.013**
WOMAC Pain Subscale	47	2.4 (4.4)	**0.001**
Actiwatch Pain Score (4 day avg)	39	0.7 (2.03)	**0.038**
Diary Pain Scores (4 day avg)	44	0.6 (1.96)	**0.053**

- **Celecoxib showed significant improvement in pain scores with all pain outcome measures**
- **Actiwatch performed similarly to In-Clinic Scores, but did better than nightly paper diaries**

Delta = difference in treatment effect (baseline – treatment) for celecoxib minus placebo (positive numbers =larger effect with celecoxib)

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Measures of Function: Celecoxib vs. Placebo (Difference from Baseline - Treatment Period 1)

Variable*	[N]	Mean Delta** (SD†)	*p-value*
WOMAC Function	25	3.3 (5.72)	0.047
Activity Score – Peak Counts/Min	22	70.1(233)	0.011

**Activity = 4 day averages to determine treatment effect (baseline – treatment) – negative numbers = increased activity. **Delta = difference in treatment effect (baseline – treatment) for celecoxib minus placebo (negative numbers =larger effect with celecoxib) † SD for Treatment.*

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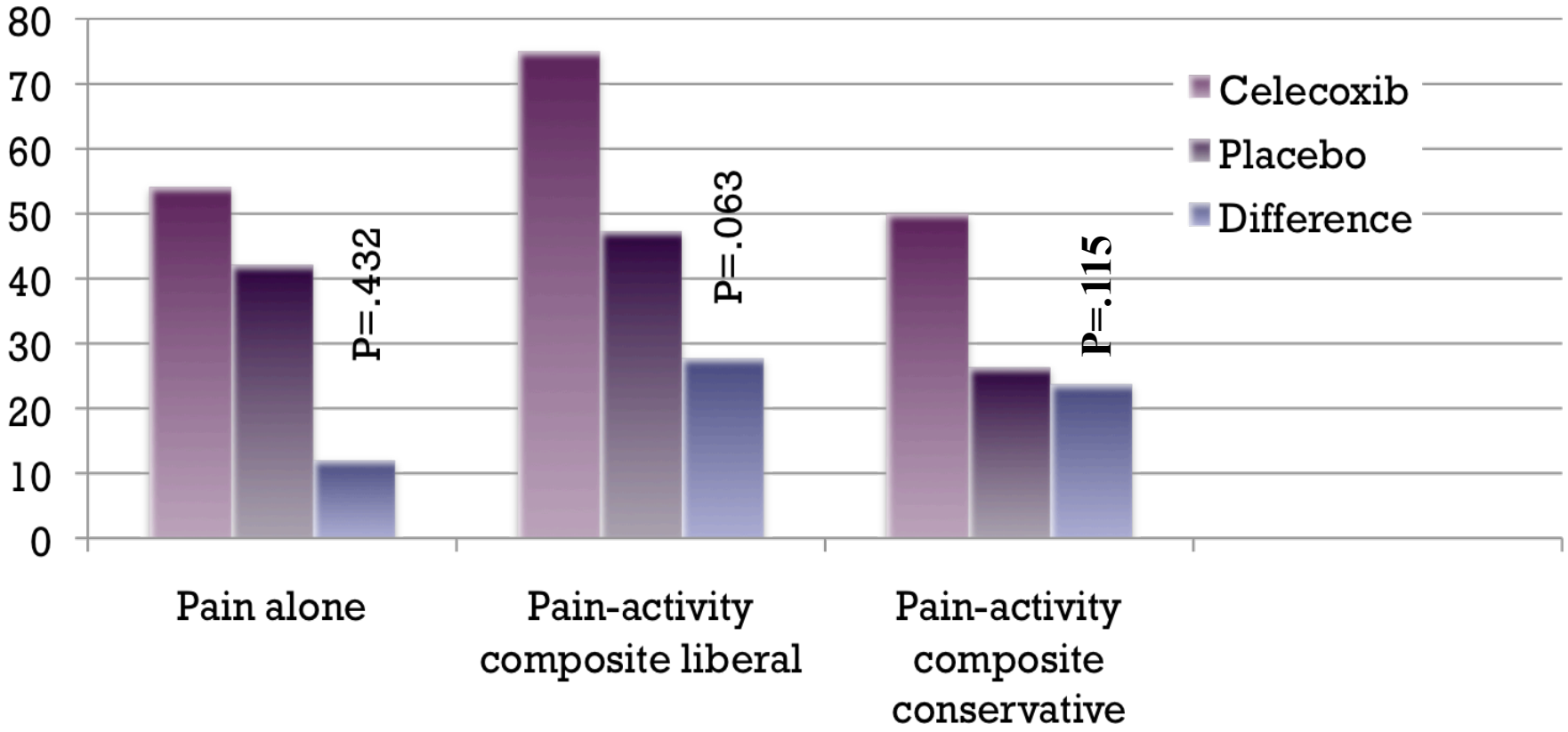
Pain-Activity Composites in an OA RCT, Celecoxib vs. Placebo, n=43



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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Actiwatch Study - Conclusions

- Chronic pain studies (at least OA) can be done efficiently at single sites
- Actiwatch actigraphy much more responsive (p=.01) than WOMAC function (p=.04) (first period analysis)
- Actiwatch QID pain scores performed similarly to In-Clinic Pain Scores but much better than paper diaries
- Pain-activity composites appeared to be more responsive than pain alone, and may provide a more valid classification of true analgesic responders than pain or activity alone

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Part 4
What now?

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Overall Conclusions

- Outcome of pain studies is not random: observed drug effect is a knowable amalgam of drug and experiment.
- Clinical trial design can be informed by quantitative analysis of influences of various factors on effect sizes in past studies
- Specific sources of error can be identified, and tools developed to reduce error
- These methods are likely to lead to efficient POC studies in single research sites and reduced failure rates of small and large clinical trials

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What can you do now?

Demonstrated

- Fewer sites
- EERW > Xover > ||
- Appropriate dosing
- Minimize concomitant and rescue meds
- Use more of your data
- Use models with track record
- 2 arms
- Time-stamped pain scores
- Active controls
- Identify and eliminate sources of variability in study conduct

Exploratory

- Better pain measures
- Screen out patients who can't report pain accurately
- Pain-activity composites
- Longer baseline periods
- Subtype patients by pain mechanism
- Invest money in methods research

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Discussion

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BACKUP

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Standardized Effect Size

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

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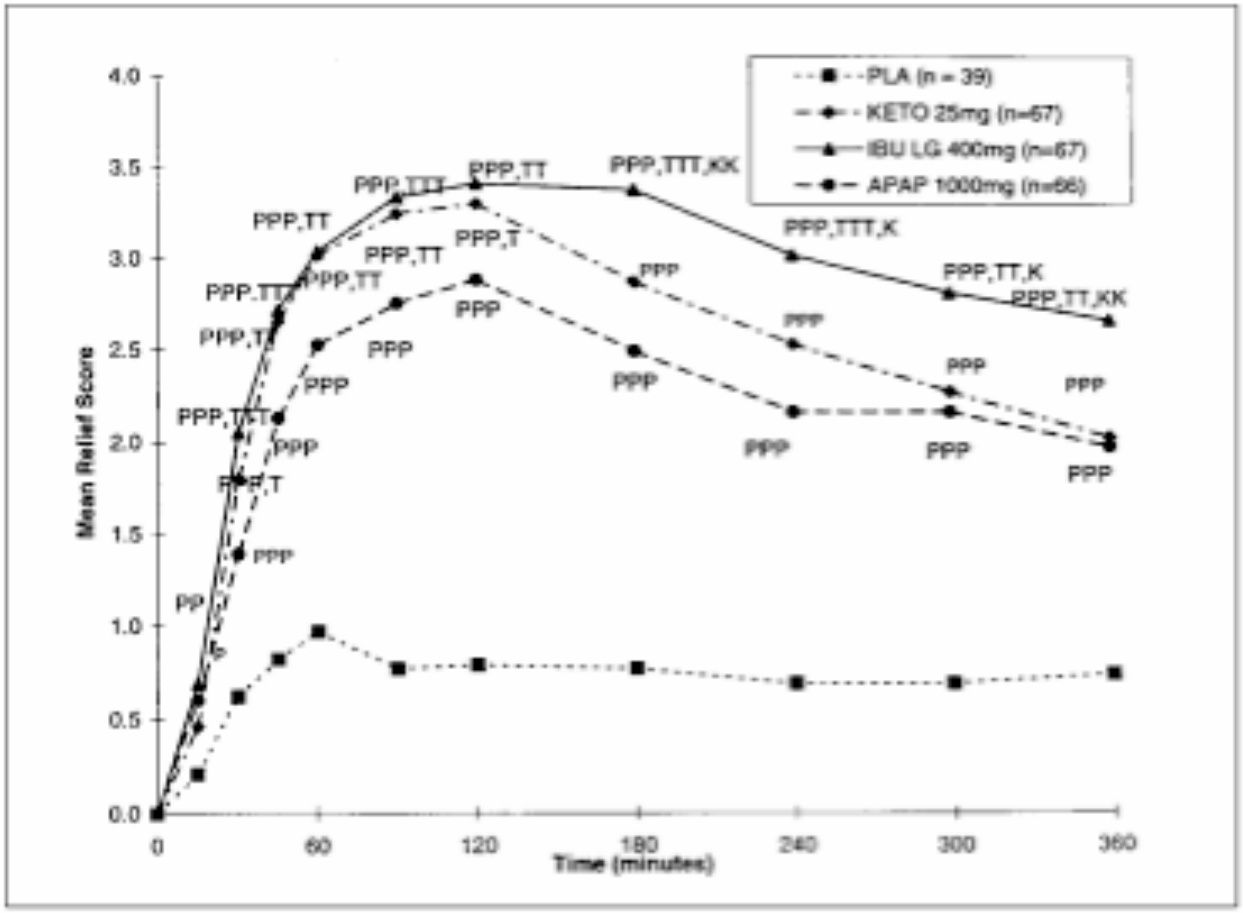

Olson N, et al, J Clin Pharm, 2001

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Table III Summary and Overall Measures of Analgesic Efficacy

Variable	Liquigel Ibuprofen, 400 mg (n = 67)	Ketoprofen, 25 mg (n = 67)	Acetaminophen, 1000 mg (n = 66)	Placebo (n = 39)
2-hour summary variables, mean (*SD*)				
SPRID2	9.18 (2.8)[a]	8.70 (2.4)[a]	7.29 (3.4)[b]	2.19 (3.2)[c]
SPID2	3.67 (1.2)[a]	3.43 (1.1)[a]	2.80 (1.5)[b]	0.76 (1.2)[c]
TOTPAR2	5.51 (1.6)[a]	5.27 (1.4)[a]	4.49 (2.0)[b]	1.44 (2.0)[c]
6-hour summary variables, mean (*SD*)				
SPRID6	29.19 (9.8)[a]	24.64 (10.4)[b]	21.67 (11.5)[b]	6.94 (11.9)[c]
SPID6	11.77 (4.2)[a]	9.64 (4.4)[b]	8.36 (4.7)[b]	2.60 (4.7)[c]
TOTPAR6	17.42 (5.7)[a]	15.00 (6.2)[b]	13.30 (7.0)[b]	4.33 (7.3)[c]
Overall assessment of study drug,* mean (*SD*)	3.12 (1.1)[a]	2.97 (1.0)[a]	2.42 (1.4)[b]	0.69 (1.1)[c]

Same letters following means indicate nonsignificant treatment differences. SPRID2, SPRID6 = summed pain relief and pain intensity difference (PRID) at 2 hours and at 6 hours, respectively; SPID2, SPID6 = summed pain intensity difference (PID) at 2 hours and 6 hours, respectively; TOTPAR2, TOTPAR6 = summed pain relief at 2 hours and 6 hours, respectively.

* Scale 0 to 4 (0 = *poor*, 4 = *excellent*).

Olson N, et al, J Clin Pharm, 2001

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Table II. Analgesic efficacy of the 4 treatment groups.

	Ibuprofen Liquigel 200 mg (n = 61)	Ibuprofen Liquigel 400 mg (n = 59)	Acetaminophen 1000 mg (n = 63)	Placebo (n = 27)
Overall analgesic effect (mean ± SE)				
TOTPAR 2 (0 to 8 scale)	5.39 ± 0.21*†	5.60 ± 0.18*‡	5.02 ± 0.29*	1.84 ± 0.40
TOTPAR 6 (0 to 24 scale)	14.72 ± 0.83*‖	16.56 ± 0.75*¶	11.99 ± 1.01	5.25 ± 1.49
SPID 2 (–2 to 6 scale)	2.52 ± 0.16*†	2.65 ± 0.15*‡	2.22 ± 0.18*	0.24 ± 0.30
SPID 6 (–6 to 18 scale)	6.93 ± 0.59*¶	8.07 ± 0.50*¶	5.05 ± 0.58	0.46 ± 1.13
Patients' global assessment (0 to 4 scale)	2.66 ± 0.13*†	2.95 ± 0.10*¶	2.29 ± 0.17*	0.85 ± 0.25
Onset of analgesic effect, min				
Meaningful relief (95% CI)	30.0* (28.8–37.2)	28.8*† (26.4–33.0)	29.4‖ (24.0–37.2)	>360 (NE)
% Experiencing meaningful relief	93	98	86	41
Confirmed first perceptible relief in patients who experienced meaningful relief, min (95% CI)	14.4‖ (11.4–19.8)	10.2*¶ (9.0–13.8)	12.0# (10.8–14.4)	>360 (NE)
% Experiencing first perceptible relief	93	98	86	41

TOTPAR 2 = total pain relief at 2 hours; TOTPAR 6 = total pain relief at 6 hours; SPID 2 = summed pain intensity difference at 2 hours; SPID 6 = summed pain intensity difference at 6 hours; NE = not estimable.

*$P < 0.001$ versus placebo.

†$P < 0.05$ versus acetaminophen 1000 mg.

‡$P < 0.01$ versus acetaminophen 1000 mg.

§$P < 0.001$ versus acetaminophen 1000 mg.

‖$P < 0.01$ versus placebo.

¶$P < 0.01$ versus ibuprofen liquigel 200 mg.

#$P < 0.05$ versus placebo.

Hersh E, et al, Clin Ther, 2000

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DOI 10.1002/art.24837

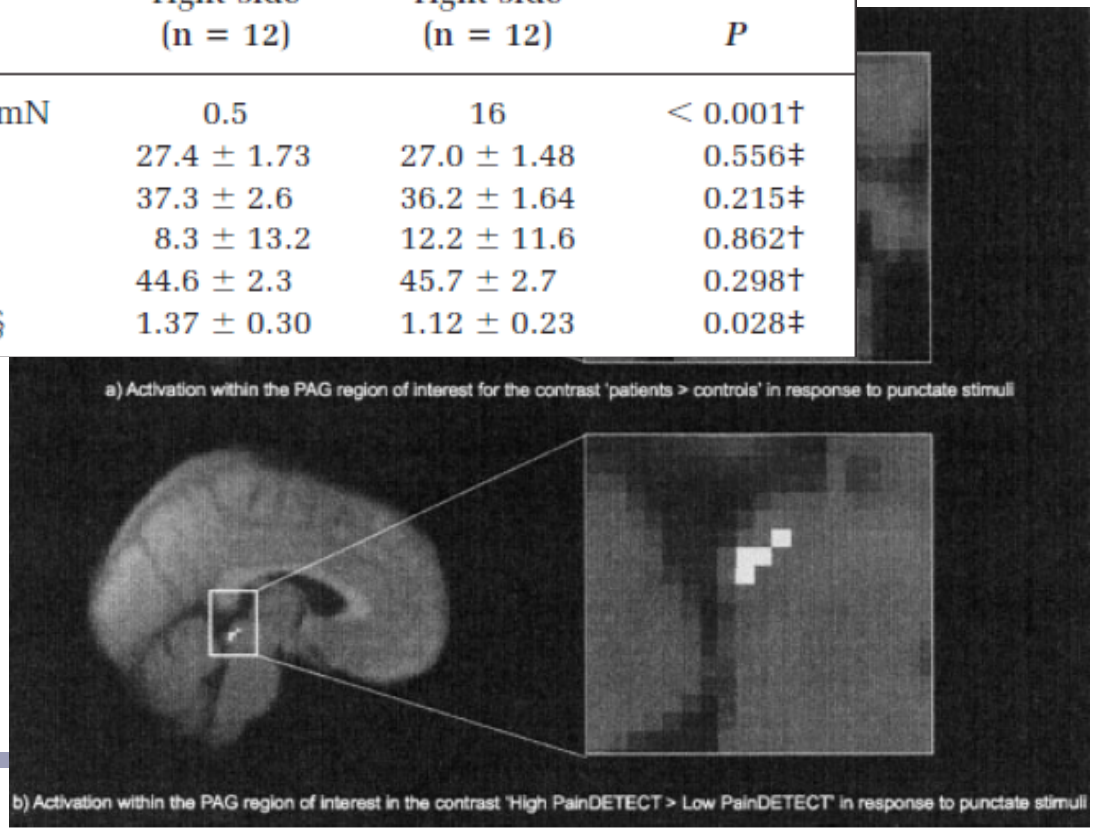
ORIGINAL ARTICLE

Psychophysical and Functional Imaging Evidence Sup in a

STEPH
BORIS

Table 1. Results of psychophysical testing performed in line with the quantitative sensory testing methods described by the German Research Network on Neuropathic Pain*

	Patients, right side (n = 12)	Controls, right side (n = 12)	*P*
Punctate detection threshold, median mN	0.5	16	< 0.001†
Cool detection threshold, °C	27.4 ± 1.73	27.0 ± 1.48	0.556‡
Warm detection threshold, °C	37.3 ± 2.6	36.2 ± 1.64	0.215‡
Cold pain detection threshold, °C	8.3 ± 13.2	12.2 ± 11.6	0.862†
Heat pain detection threshold, °C	44.6 ± 2.3	45.7 ± 2.7	0.298†
Sharpness of 256-mN stimulus (log_{10})§	1.37 ± 0.30	1.12 ± 0.23	0.028‡



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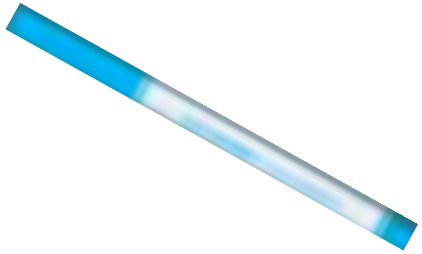
Bedside Sensory Testing Kit



ANALGESIC SOLUTIONS

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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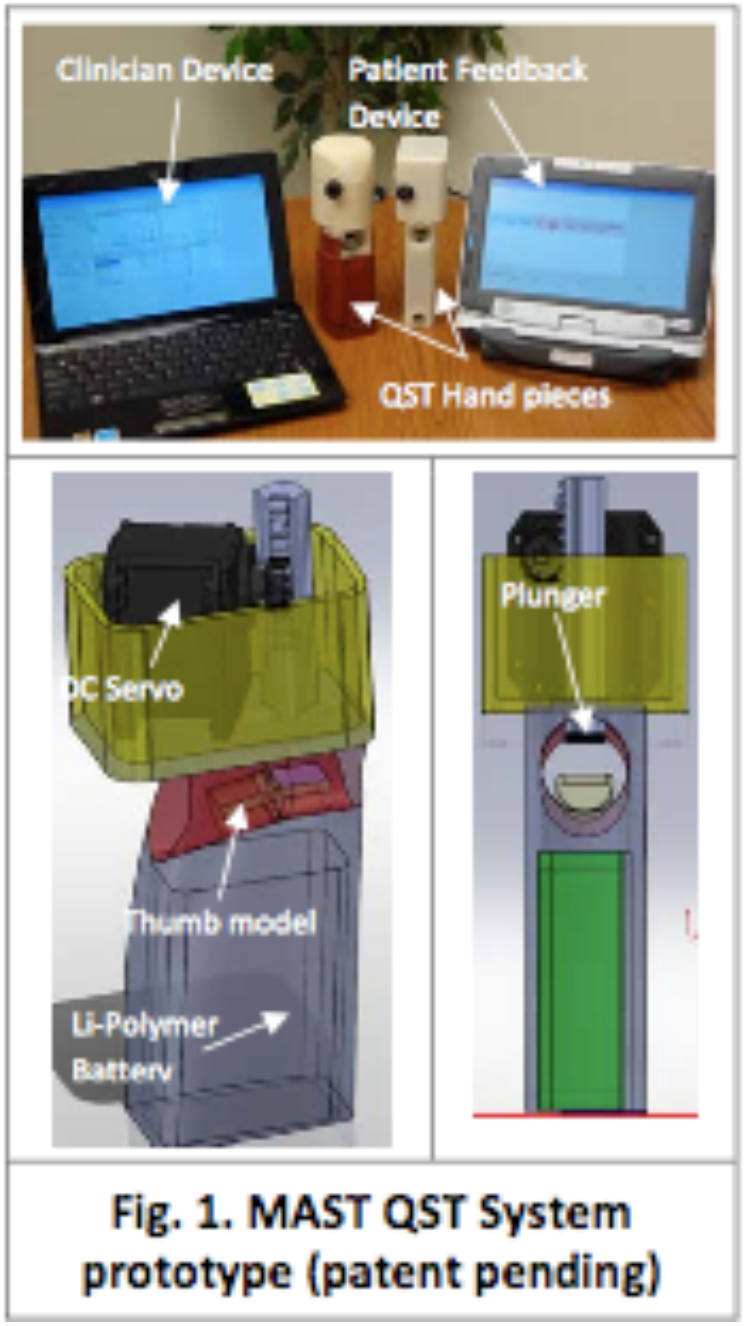

Fig. 1. MAST QST System prototype (patent pending)

Pre- vs. Post-Exercise Pain in 65 subjects with OA

All subjects indicated verbally that their pain had worsened after exercise.

Responder Sample	Pre	Post	Delta	SES	
VAS(100mm)	48.30 mm (±24.50)	51.6 mm (±29.40)	3.3	.12	p>.05
PM(°C)	41.19°C (±5.45)	43.81°C (±5.73)	2.6	.46	P<.001

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Validity - Reliability